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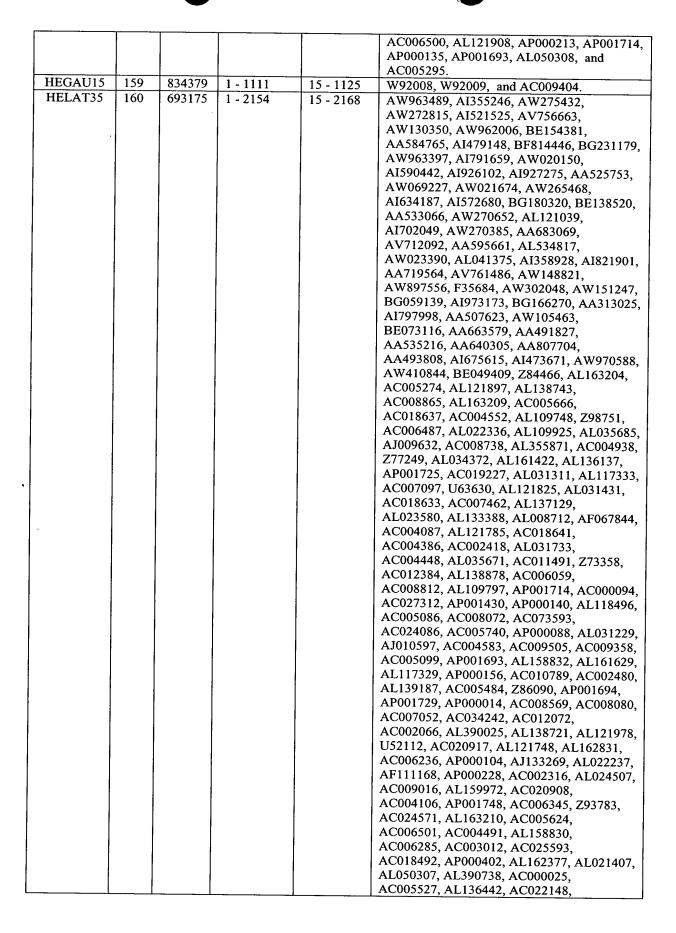
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	1	1			T34609, AA215954, H23218, AW050688,
	1	1			H24734, AW514476, AA923801, H66432,
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					AA707618, H24733, R87113, T27438,
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HLWIJB04	24/	030099	1 - 790	13 - 804	
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	į			:	AU135631, N51624, AW440717, AU156188,
	ļ	ļ			AI244310, BF934257, AU137679, AU135523,
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					AW050812, BE871104, AA664347,
				!	AV659324, BF219419, AA838720, T74688,
				l	AW176080, C75117, AI400510, AA100857,
				1	BE018093, AA056968, BE819468,
					AV693575, AV692481, AV645491, N54246,
					AA481324, AI880359, BE772570, AV692975,
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					AI394339, AV645442, BE819545, AV694085,
					AV694699, AV653729, AA281439,
					AA486172, AA468902, BE939493,
					AV719793, AV695940, AI751877, AV660065,
					T95295, AA359423, D20113, BF379099,
					AA643688, BE819461, BE831675,
					AW854105, AA385681, T95375, AI890004,
	:				AA359712, AA057016, N58703, AW071048,
1					T74801, R50203, AW054934, Z19305,
					T64005, BE716219, AI635828, AI928438,
					AA602300, AI685551, BE301581, T36144,
					R40496, AI262366, AA133917, AW970142,
					AA514233, BE819546, AW970145,
					AV716521, BF752093, W45353, AA315963,
					BF912723, AI273020, T86288, AW768388,
					AA533897, T90950, AA486109, R50150,
					AW273588, T86387, AI635443, T85836,
					AA587303, BF359777, AA353447, BE839081,
					T98225, R13065, T64084, AA353040,
	1				AA383720, AA513774, BE819498, BF771959,
					AW945448, AA669130, AI872115, AI367142,
					AI758444, T27349, BE008461, BE819456,
	1				AW467705, AA253283, AW316697, W15319,
				·	AI819151, AI571469, AA382189, BF359773,
	1				AA361822, AA130233, AI557206, BE831556,
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					D82703, BF000110, BF678342, BF359762,
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					AF174535, and D82662.
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HMCAZ04	267	88/443	1 - 1/21	15 - 1/35	AI133370, AV716073, BF027170, AW024415, AI302184, BG120804, AV692708, AW955102, BF108769, BF691126, BE264000, AW273859, AV700904, AV699357, BE386262, BG169469, BE789575, AA948547, AI299954, BG236229, AW043839, AV685386, AW516856, AV688204, BE546468, AA639665, AA911904, BE819542, AW119093, AI097457, AI522298, AI222830, BE819457, BE819514, BE839222, BE819567, AW182738, BE819505, BG170954, AI305813, AA526991, AA527252, W96028, BE839045, BE819511, AA280758, BE831532, N50841, BE790051, AA643646, BF371410, AI290542, BE674172, BE819590, BE819554, W94661, AI240325, AI751876, BE871104, AI290551, AI300130, AA885922, AA664347, AW050812, AV659324, BF219419, AV645491, AA838720, T74688, AV693575, AV692481, AW176080, C75117, AI400510, AA100857, BE018093, AV692975, AA056968, BE819468, N54246, AV645442,
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HMCAZ04	267	88/443	1 - 1/21	15 - 1/35	AI133370, AV716073, BF027170, AW024415, AI302184, BG120804, AV692708, AW955102, BF108769, BF691126, BE264000, AW273859, AV700904, AV699357, BE386262, BG169469, BE789575, AA948547, AI299954, BG236229, AW043839, AV685386, AW516856, AV688204, BE546468, AA639665, AA911904, BE819542, AW119093, AI097457, AI522298, AI222830, BE819457, BE819514, BE839222, BE819567, AW182738, BE819505, BG170954, AI305813, AA526991, AA527252, W96028, BE839045, BE819511, AA280758, BE831532, N50841, BE790051, AA643646, BF371410, AI290542, BE674172, BE819590, BE819554, W94661, AI240325, AI751876, BE871104, AI290551, AI300130, AA885922, AA664347, AW050812, AV659324, BF219419, AV645491, AA838720, T74688, AV693575, AV692481, AW176080, C75117, AI400510, AA100857, BE018093, AV692975, AA056968, BE819468, N54246, AV645442, AA481324, AI880359, BE772570, AV694085, AV694699, AV653729, AI394339, BE819545, AA486172, AA281439, AA468902, AV695940, AI751877, BE939493, AV719793, AV660065, T95295, AA643688, AA359423,
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	i				AA452189, AW854101, BE279938,
		E			BG116638, AV683681, BE563147, BE388057,
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HMICI80	278	827318	1 - 1758	15 - 1772	AW206437, AI681626, AW590679,
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HNECW49	296	639117	1 - 475	15 - 489	Al 110040.
HNEDH88	297	815675	1 - 2059	15 - 2073	H00176 H00927 A1016452
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HNGKT41	314	836061	1 - 1034	15 - 1048	AW862214, AW859811, and AW862215.
HNGMW45	315	838613	1 - 1516	15 - 1530	
HNGNK44	316	834949	1 - 1164	15 - 1178	T71076, T71014, BE767503, BE767495,
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HNGNO53	317	836063	1 - 811	15 - 825	R37935.
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HSDZM54	393	637870	1 - 540	15 - 554	AI751079, AV700614, AI682030, BF688845, AA665727, AC000159, and AB007864. AV729255, AI535959, AV726938, AV701879, AV729339, AV654282, AV725709,
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HSDZM54	393	637870	1 - 540	15 - 554	AI751079, AV700614, AI682030, BF688845, AA665727, AC000159, and AB007864. AV729255, AI535959, AV726938, AV701879, AV729339, AV654282, AV725709, AV705433, AV702947, AV691890, AV662257, AV705443, AV706584,
HSDZM54	393	637870	1 - 540	15 - 554	AI751079, AV700614, AI682030, BF688845, AA665727, AC000159, and AB007864. AV729255, AI535959, AV726938, AV701879, AV729339, AV654282, AV725709, AV705433, AV702947, AV691890, AV662257, AV705443, AV706584, AV725529, AV728243, AI557222, AV726503,
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HSDZM54	393	637870	1 - 540	15 - 554	AI751079, AV700614, AI682030, BF688845, AA665727, AC000159, and AB007864. AV729255, AI535959, AV726938, AV701879, AV729339, AV654282, AV725709, AV705433, AV702947, AV691890, AV662257, AV705443, AV706584, AV725529, AV728243, AI557222, AV726503, AV709039, AV692176, AV758197, BF942332, BG222560, BG222322, AV738071, AA469321, BE880733,
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HSDZM54	393	637870	1 - 540	15 - 554	AI751079, AV700614, AI682030, BF688845, AA665727, AC000159, and AB007864. AV729255, AI535959, AV726938, AV701879, AV729339, AV654282, AV725709, AV705433, AV702947, AV691890, AV662257, AV705443, AV706584, AV725529, AV728243, AI557222, AV726503, AV709039, AV692176, AV758197, BF942332, BG222560, BG222322, AV738071, AA469321, BE880733, AV717185, BE881230, BE879882, BE875275,

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HT1SC27	416	630647	1 - 1184	15 - 1198	AW963760, AI085450, AA380828,
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HT4FV41	HT3BF49	417	838620	1 - 2160	15 - 2174	AW450103, AI286250, H15073, H15072, AI283763, AW451893, and AL355304.
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HTEED26	429	762846	1 - 2165	15 - 2179	BF980309, AA883424, and AB050260.
HTEED26	430	753425	1 - 2153	15 - 2167	
HTEEF26	431	789606	1 - 1001	15 - 1015	AL532273, BE798143, BE799576, BE799205, BE744642, BF981471, BF965619, AU122163, BG250643, BE618090, BE798861, AU133515, BE271977, AW026449, AW961324, AA503549, AI127746, AI857656, BG120363, AA992599, AI095033, AV738369, AA635176, AA826399, AA631375, AW513797, AA872323, AW079855, AA373024, AA432393, AA431719, AL534237, F31544, AA362778, BF572211, AW797087, AA035646, AW075535, BF791432, AA076684, AI351830, AA303611, BE844046, AI942243, AW381507, AI872998, AA484183, AK024179, AK023287, AC006329, and AL157469.
HTEEF26	432	879704	1 - 1259	15 - 1273	AL532273, BE798143, BE799576, BE799205, BE744642, BF981471, BF965619, AU122163, BG250643, BE618090, BE798861, AU133515, BE271977, AW026449, AW961324, AA503549, AA992599, AI127746, AI857656, BG120363, AI095033, AA635176, AV738369, AA826399, AA631375, AW513797, AA872323, AW079855, AA373024, AA432393, AA431719, AL534237, F31544, AA362778, BF572211, AW797087, AI004788, AA035646, AW075535, BF791432, AA076684, AI351830, AA303611, BE844046, AI942243, AW381507, BE045227, AI872998, AA484183, AU154803, AK024179, AK023287, AL157469, and AC006329.
HTEEW69	433	764835	1 - 1268	15 - 1282	BE253978, BE254398, BE781341, BE255799, BE780436, BE780457, BE255033, BE251940, BE257706, BE780314, BE783528, BE255909, AA887084, AW172618, BE253356, BE257391, BE257100, AA913157, BE252558,

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	1				A70867, AR062872, AR093385, AR008408,
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HTEGS11	435	862066	1 - 967	15 - 981	AW952408, BF515910, AI050882, AI480168,
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HTEHA56	436	806461	1 - 1388	15 - 1402	AL534825, BF966655, BF220011,
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					AU148467, AI983228, AI949855, BE858463,
					AU158916, AV751641, AU151009,
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AL530660, AL120983, AW365846, BE141392, AI276663, BG121604, BF857983,	HTEMQ17	440	840387	1 - 1754	15 - 1768	· · · · · · · · · · · · · · · · · · ·
BE141392, AI276663, BG121604, BF857983,						
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HTENR63	441	877952	1 - 1577	15 - 1591	AL514834, AL519774, AL519775,
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		İ			AK000652, AK026464, AK026504,
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					AK026583, AK000647, AL137550,
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		-			AK000083, AF111849, AF116602,
	1	ĺ			AK026647, AL137488, AF026816, AF321617,
	İ	ľ			AK026533, AK027113, AL049466,
	<u> </u>				AL137526, AF116644, and AK026526.
HTGGM44	442	842856	1 - 3002	15 - 3016	AW974580, BE764084, AA651951, W01997,
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HTHBZ06	443	832477	1 - 609	15 - 623	BG107523, BG180234, BF668800, AL514985,
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					AW262875, BE906621, AW470063,
					AI758577, BE907206, AA777509, AV715444,
		i			AW131846, AA406614, AW087747,
					AI811951, AI371781, AI742506, AI337891,
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					AI087379, AI792601, AI952545, AI245243,
					BG026067, AI805770, AA600140, AI040546,
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					AI934133, AW512971, BF542108, C16184,
					C16080, R78608, F05286, AI269595,
					AW800298, AA021044, C16548, AA315033,
					R46768, R35721, BE885010, BF870311,
					R25875, F02653, BF675020, AA761420,
					F22486, D57610, F00189, AA906821,
					BF028115, BF081348, AW367390, BE465797,
					Z24901, AW963734, C16270, AA527113,
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	ĺ				C16334, AI273095, AA833555, AA479334,
					AA657967, AV748779, BE737983,
	-	1			AW972454, AI857650, BE925004, D11915,
	•			İ	AA479335, D12263, AA165042, BF379271,
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		ļ			AV646354, D12285, AW954020, AW085952,
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TITE A DCA	144	602012	1 1070	45 4005	AL139184, and U10249.
HTLAP64	444	603913	1 - 1078	15 - 1092	AI940777, BF340701, AI417805, AA328338,
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	<u> </u>				and AC004556.
HTLBT80	445	840045	1 - 2087	15 - 2101	AL519674, AL518564, AL530114, AL524125,
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					BG248163, BE869185, BE893350, BF435225,
					BE905414, BG026633, BF033083, BF970046,
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					AI420163, BE550276, AI949071, AW963076,
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	İ	1			AW473585, AI674961, BE868575, AI247090,
	ł				H08477, AA576510, BE391031, H06603,
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		1			BG152437, AA814595, AI569050, AI239612,
		•			H06633, AI623626, R69764, AA971138,
					H07140, BE856299, AI357631, AI001995,
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					H52166, AA026966, BF988194, W22979,
		ļ			BF372164, H89737, R87305, BF677308,
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HTLDA84	446	686397	1 - 1430	15 - 1444	AA449997, AV758870, AV761107,
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				AC007225, AC005081, AL138976,
				AC007637, AC006252, AC011475,
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HTODH57	466	823126	1 - 1638	15 - 1652	AL136531.
HTODH83	467	580884	1 - 1967	15 - 1981	
HTOEV16	468	853616	1 - 1626	15 - 1640	BF527726, BE299173, AA887221, AI928947,
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				-	AI537927, AA722267, BE295289, H18455,
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					AI870950, AI378717, AI311219, AW007384,
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HTOGR38	469	824639	1 - 762	15 - 776	AI287599, N33389, AI653368, AA256934,
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НТОНО21	470	732808	1 - 713	15 - 727	AI821139, AI791153, BE562162, AW601890,
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					AF126008, U03634, and AF127481.
НТОНQ05	471	853621	1 - 1846	15 - 1860	AI891064, AV712559, AV714449, BE674242,
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	-				AA579913, AW087343, AI640380, AI337611,
					N22030, AW339605, AI278579, AI268795,
	Ì				AW467495, AW076032, AI000587,
					AW440842, AI803881, AW195312,
					AA554703, BF897815, AA705051,
					AW380658, AI925062, BF356296,
					AW467476, AI587383, AI926675,
					AW341744, AW028424, BE617809,
					BE305000, AW339609, AI499956, N63943,
1					AI707579, AI270555, AW236183, AA703103,
					AI354246, BF897823, W04167, AI247317,
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					AW818146, AA316763, AV750915,
					BG166024, BF126365, AW818168,
					AA553442, AW961194, AU139829,
					AA721044, BE972551, C75547, AW852366,
					AA663375, AW895721, AA169131,
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					C75519, AA307312, AW891047, AW129720,
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					AA225408, F33455, T03280, AA218836,
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AA180028, BE146572, AW864686, AL043280, BF993214, AW176108, AA602337, AU135145, AW936347. AW818166, BE178630, BE160554, AA315418, AA225390, AU120914, AW089702, AA164938, BF931499, AV720960, AA668376, AW993580, AA088381, AA487131, N23850, AA683281, AL119296, C75667, AI791133, AA586720, AA744577, AA121904, AA663524, AA557997, AW075927, AA584519, BF985200, AA715198, AA780853. AV655231, T02882, AA487154, AA490027, AA613166, W90195, BF756980, AL134345, AA577726, BF940866, AA714323, AA864766, AA669373, AA680217, AA641592, AA481772, AA464942, BF876083, AA714539, AA053383, AA180278, BG005346, AA669032, AA582583, BF883155, AA213637, AA679355, AL120645, AA577842, N57818. AA586652, AA583358, AA669383, AL119618, AA315673, AA489776, AW850913, AA494169, AA669164. AA489883, AW850912, N27645, AA594077, AA614210, AA551059, AA218892, AW835453, AA167533, AA651944. AL134095, H64879, AV686720, BF912775, AA584801, AV696238, AA485972, AA744267, BF672307, AW835452, AA481764, AW892505, AA834022. BE967439, AA161346, AK021968, AC002524, AC019173, AC009487, AC022143, AL121717, AL009176, AC025588, AL356438, AP002529, AB042031, AL136298, Z94056, AC007250, AC010369, AC005076, AC083875, AC002349, AP000083, AC005177, AC008664, AL356215, AL356020, AP000515, AC012598, AC006356, AL158193, AL133549, AC007344, AL121999, AL049710, AL136125, AL137800, AC007567, AL079305, AL136164, AC021070, AL445068. AC006070, AF241732, AC020655, AJ239329, AL390146, AC006516, AL133214, AL138816. AC008444, AL031599, AP000034, AC087089, AC005199, AC006029, AL161440, AC004158, AC004535, AL096827, AC023128, AC005922, AC008009. AL359204, AP000220, AC004894, AL136308, AC004527, AL354833, AL121841, AC019187, AJ271736, AJ225782, AC016689, AC066590, AL445224, AC000055, AL020990, AL021068, AL117667, AC003081, AC007239, Y10196, AL022345, AL138900, AL022241, AC006288, AL022154, AL353747, AL445439, AL031393, AC004613, AC016956, Z82899, AL118496, AL390316, AL158206, AL022727, AC016572, AL356774, Z76735, AL139279, AL390759, AC009892, AL023693, AL133162, AC061958, Z97198.

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HTOJL95	473	762851	1 - 1933	15 - 1947	AU121033, AU140348, AA533107, AI554666,
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HTTCB60	476	637720	1 - 1243	15 - 1257	BF843130, AU117513, AI681088, AI680701, AI361919, AW157408, C04469, AI955119, AI928912, AI469126, BF116057, AI889802, AV729134, AW162400, BF337597, AW895617, AA863008, AI417558, AW057928, AI815549, AA371959, AW327982, AI678991, H84469, BE382373, R89704, H83576, AV721961, AI753112, AW960529, AW970050, AA416603, AV703569, D53506, AI160829, AA570262, D56033, AI902757, W28382, D55124, AW327983, AV704116, BE771726, AA678993, AA626015, BF677512, AI220523, AI804192, H58710, BF834065, AW961885, C04546, AI816491, BF432083, AW900853, AA974795, AA971398, AA416621, AA916174, AI538211, AA864450, AA909154, AA302583, BF809398, BF196301, AW181916, AU144323, AI123339, AA372034, R37820, H43815, M78721, C04507, H49972, BE932208, AW901234, AW901364, AI565159, AW341471, AA601597, R95024, R94938, H92470, AI799873, D55563, H50010, AA702558, AA574290, AW900864, AW905864, BG015591, R96005, AW903806, R95966, H30648, H20798, T63337, BE243401, AA707707, H27871, BF979913, BF991086, H14147, H30647, H58320, T61965, H56594, H22616, T63962, BE910629, R88595, M78801, H56595, AL036957, BG009728, AA505362, AI915406, BE829368, BE770916, AA977550, BE272026, BF844035, AA910693, AA832013, C20841, BG031911, AF135372, AK021522, AJ225044, I77040, AJ133104, AF240769, AL050223, AF007168, U60150, M36203, X76199, and M36204. AL527596, AL530567, AI114859, BE407719, AL527597, AL529809, AI830718, AI640304, BF447073, AI862404, AI419019, BE899304, AA496239, AI889002, AL514080, BF000126, AI200382, BE048538, AA442132, AI798632, AI140806, AI565622, AU156790, AA834046, AW294987, AI183801, W68566, AI872891, AA456203, AI364465, AI765479, BE645691, AI468507, BF477789, AI672711, W68567, AI468507, BF477789, AI672711, W68567, AI468507, BF477789, AI672711, W68567, AI468507, BF477789, AI672711, W68567, AI468507, BF477789, AI672711, W68567, AI468507, BF477789, AI672711, W68567, AI468507, BF477789, AI672711, W68567, AI468507, BF477789, AI672711, W68566,
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HTTEE41	477	840950	1 - 1959	15 - 1973	
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HTTTTT	470	70205=	4533		T27335, and T27402.
HTTEZ02	478	702027	1 - 1866	15 - 1880	Z78400, BG028169, AV701245, BF217849,
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HTXBD09	480	839429	1 - 1907	15 - 1921	AI884916, AW083150, AA827694, W93788,
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		ŀ			BE770147, BE868866, AA293602, BE044456,
	ľ				AI382144, AA421693, R15900, AI498767,
		1			AA744574, H11070, AA573099, AI160106,
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			ŀ		AI245968, AA147171, AW438652,
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HTXKF95	489	834438	1 - 870	15 - 884	AI934965, AW574868, BF056901, BE676636, AA831751, AA814605, AW590381, AI857985, AA742405, BF592924, AI697328, BF059191, AW450001, AI341301, AW610280, AI635420, AA917582, AI418901, C01813, BE694168, AW291415, AA775165, BF798709, BF916068, BF798708, AC008083, and AC004242.
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BF244825, AA888168, F03832, C04718,
AA534374, BE297735, R50403, R56826,
R81871, T33719, AI569605, N41917,
AW731635, AW050454, BF737093, Z44868,
AI648412, T06476, AA428005, W37625,
BF893080, BF820895, BF769768, F07587,
F01530, D54185, AI611777, AA902145,
AA338785, Z25279, BE617105, F00464,
AA084935, BE241564, R10512, AI627173,
BE252263, AA022983, AV743083,
BE940174, N75173, BE929227, H28878,
AA094149, AW294418, AI261764,
AA449769, T63873, AI885556, AA775981,
BE710635, BE936751, AR062110, AL117480,
AL132825, AF055022, AL096738, AF130458,
AR069619, AF130459, and AF130460.

TABLE 4

Code	Description	Tion	1.0	LG nr:		1
Code	Description	<u>Tissue</u>	<u>Organ</u>	Cell Line	<u>Disease</u>	<u>Vector</u>
AR022	a_Heart	a_Heart				
AR023	a_Liver	a_Liver				
AR024	a_mammary gland	a_mammary gland				
AR025	a_Prostate	a_Prostate				
AR026	a_small intestine	a_small intestine				
AR027	a_Stomach	a_Stomach				
AR028	Blood B cells	Blood B cells				
AR029	Blood B cells activated	Blood B cells				
4 D 000		activated				
AR030	Blood B cells resting	Blood B cells resting				
AR031	Blood T cells activated	Blood T cells activated				
AR032	Blood T cells resting	Blood T cells resting				
AR033	brain	brain				
AR034	breast	breast				
AR035	breast cancer	breast cancer				
AR036	Cell Line CAOV3	Cell Line CAOV3				
AR037	cell line PA-1	cell line PA-1		_		
AR038	cell line transformed	cell line				
AR039	colon	transformed				
AR040	colon (9808co65R)	colon colon				· .
		(9808co65R)				
AR041	colon (9809co15)	colon (9809co15)				
AR042	colon cancer	colon cancer				
AR043	colon cancer (9808co64R)	colon cancer (9808co64R)				
AR044	colon cancer 9809co14	colon cancer 9809co14				
AR045	corn clone 5	corn clone 5				
AR046	corn clone 6	corn clone 6				
AR047	corn clone2	corn clone2				
AR048	corn clone3	corn clone3				
AR049	Corn Clone4	Corn Clone4				
AR050	Donor II B Cells 24hrs	Donor II B Cells 24hrs	-			
AR051	Donor II B Cells 72hrs	Donor II B Cells 72hrs				
AR052	Donor II B-Cells 24 hrs.	Donor II B-Cells 24 hrs.				
AR053	Donor II B-Cells 72hrs	Donor II B-Cells				
AR054	Donor II Resting B Cells	72hrs Donor II Resting B Cells				
AR055	Heart	Heart				
AR056	Human Lung (clonetech)	Human Lung		- 		
		(clonetech)				
AR057	Human Mammary	Human				
	(clontech)	Mammary (clontech)				
AR058	Human Thymus	Human Thymus				

	(clonetech)	(clonetech)	1	1		1
AR059	Jurkat (unstimulated)	Jurkat			 	
	(anomination)	(unstimulated)				
AR060	Kidney	Kidney	1			
AR061	Liver	Liver				
AR062	Liver (Clontech)	Liver (Clontech)				
AR063	Lymphocytes chronic	Lymphocytes		1		
	lymphocytic leukaemia	chronic				
		lymphocytic	Ī	ŀ	ł	
AR064	Lymphocytes diffuse large	leukaemia Lymphocytes				
AROUT	B cell lymphoma	diffuse large B]	
	2 con tymphoma	cell lymphoma				
AR065	Lymphocytes follicular	Lymphocytes				
	lymphoma	follicular				
		lymphoma				
AR066	normal breast	normal breast				
AR067	Normal Ovarian	Normal Ovarian				
AR068	(4004901) Normal Ovary 9508G045	(4004901)				
AKUU	Normal Ovary 9508G045	Normal Ovary 9508G045				
AR069	Normal Ovary 9701G208	Normal Ovary		 	 	
	1.0111mi Ovary 7/010200	9701G208	1			
AR070	Normal Ovary 9806G005	Normal Ovary				
		9806G005				
AR071	Ovarian Cancer	Ovarian Cancer				
AR072	Ovarian Cancer	Ovarian Cancer				
	(9702G001)	(9702G001)				
AR073	Ovarian Cancer	Ovarian Cancer				
AR074	(9707G029) Ovarian Cancer	(9707G029)				
AKU/4	(9804G011)	Ovarian Cancer (9804G011)				
AR075	Ovarian Cancer	Ovarian Cancer				
	(9806G019)	(9806G019)				
AR076	Ovarian Cancer	Ovarian Cancer				
	(9807G017)	(9807G017)				
AR077	Ovarian Cancer	Ovarian Cancer				
12020	(9809G001)	(9809G001)				
AR078	ovarian cancer 15799	ovarian cancer		,		
AR079	Ovarian Cancer	15799 Ovarian Cancer				
AKU/9	17717AID	17717AID				
AR080	Ovarian Cancer	Ovarian Cancer				
	4004664B1	4004664B1				
AR081	Ovarian Cancer	Ovarian Cancer				
	4005315A1	4005315A1				
AR082	ovarian cancer 94127303	ovarian cancer				
1.000		94127303				
AR083	Ovarian Cancer 96069304	Ovarian Cancer		1		
AR084	Ovarian Cancer 9707G029	96069304				
7.004	Ovarian Cancer 9/0/0029	Ovarian Cancer 9707G029				
AR085	Ovarian Cancer 9807G045	Ovarian Cancer				
		9807G045				
AR086	ovarian cancer 9809G001	ovarian cancer				
		9809G001				
AR087	Ovarian Cancer	Ovarian Cancer				
A DOGG	9905C032RC	9905C032RC				
AR088	Ovarian cancer 9907 C00	Ovarian cancer				
ADOOD	3rd Prostate	9907 C00 3rd				
AR089 AR090	Prostate (clonetech)	Prostate				
ANUSU	1 rostate (Cionetecti)	Prostate (clonetech)				
AR091	prostate cancer	prostate cancer				
AR092	prostate cancer #15176	prostate cancer				

		#15176		ļ		
AR093	prostate cancer #15509	prostate cancer #15509	:			
AR094	prostate cancer #15673	prostate cancer #15673				
AR095	Small Intestine (Clontech)	Small Intestine (Clontech)				
AR096	Spleen	Spleen				
AR097	Thymus T cells activated	Thymus T cells			<u> </u>	
	-	activated				
AR098	Thymus T cells resting	Thymus T cells resting				
AR099	Tonsil	Tonsil			· · · · · ·	
AR100	Tonsil geminal center centroblast	Tonsil geminal center centroblast				
AR101	Tonsil germinal center B	Tonsil germinal		 		
ARIOI	cell	center B cell				
AR102	Tonsil lymph node	Tonsil lymph node				
AR103	Tonsil memory B cell	Tonsil memory B			-	
		cell				
AR104	Whole Brain	Whole Brain				
AR105	Xenograft ES-2	Xenograft ES-2				
AR106	Xenograft SW626	Xenograft				
17110	~~~	SW626				
AR119	001: IL-2	001: IL-2				
AR120	001: IL-2.1	001: IL-2.1				
AR121	001: IL-2_b	001: IL-2_b				
AR124	002: Monocytes untreated (1hr)	002 : Monocytes untreated (1hr)				
AR125	002 : Monocytes untreated	002 : Monocytes			i	***************************************
	(5hrs)	untreated (5hrs)				
AR126	002: Control.1C	002: Control.1C				
AR127	002: IL2.1C	002: IL2.1C				
AR130	003 : Placebo-treated Rat	003 : Placebo-				
	Lacrimal Gland	treated Rat			ŀ	
		Lacrimal Gland				
AR131	003 : Placebo-treated Rat	003 : Placebo-				
	Submandibular Gland	treated Rat				,
		Submandibular Gland				
AR135	004 : Monocytes untreated	004 : Monocytes				
	(5hrs)	untreated (5hrs)				
AR136	004 : Monocytes untreated	004 : Monocytes				
	1hr	untreated 1hr				
AR139	005: Placebo (48hrs)	005: Placebo				
4 D 1 40	006 (14 (24)	(48hrs)				
AR140	006: pC4 (24hrs)	006: pC4 (24hrs)				
AR141	006: pC4 (48hrs)	006: pC4 (48hrs)		ļ		
AR152	007: PHA(1hr)	007: PHA(1hr)		ļ		
AR153	007: PHA(6HRS)	007: PHA(6HRS)				
AR154	007: PMA(6hrs)	007: PMA(6hrs)				
AR155	008: 1449_#2	008: 1449_#2				
AR161	01: A - max 24	01: A - max 24				
AR162	01: A - max 26	01: A - max 26				
AR163	01: A - max 30	01: A - max 30				
AR164	01: B - max 24	01: B - max 24				
AR165	01: B - max 26	01: B - max 26				
AR166	01: B - max 30	01: B - max 30				
AR167	1449 Sample	1449 Sample				
AR168	3T3P10 1.0uM insulin	3T3P10 1.0uM insulin				
AR169	3T3P10 10nM Insulin	3T3P10 10nM				
AN107	2121 TO TOMAL HISUIH	212110 10HM		L		

		Insulin			
AR170	3T3P10 10uM insulin	3T3P10 10uM insulin			
AR171	3T3P10 No Insulin	3T3P10 No Insulin			
AR172	3T3P4	3T3P4	 	 	
AR172					
	Adipose (41892)	Adipose (41892)		<u> </u>	
AR174	Adipose Diabetic (41611)	Adipose Diabetic (41611)		!	
AR175	Adipose Diabetic (41661)	Adipose Diabetic (41661)			
AR176	Adipose Diabetic (41689)	Adipose Diabetic (41689)			
AR177	Adipose Diabetic (41706)	Adipose Diabetic (41706)			
AR178	Adipose Diabetic (42352)	Adipose Diabetic (42352)			
AR179	Adipose Diabetic (42366)	Adipose Diabetic (42366)			
AR180	Adipose Diabetic (42452)	Adipose Diabetic (42452)			
AR181	Adipose Diabetic (42491)	Adipose Diabetic (42491)			
AR182	Adipose Normal (41843)	Adipose Normal (41843)			
AR183	Adipose Normal (41893)	Adipose Normal (41893)			
AR184	Adipose Normal (42452)	Adipose Normal (42452)			
AR185	Adrenal Gland	Adrenal Gland	†		
AR186	Adrenal Gland + Whole	Adrenal Gland +			
AR187	Brain B7(1hr)+ (inverted)	Whole Brain B7(1hr)+			
		(inverted)			
AR188	Breast (18275A2B)	Breast (18275A2B)			
AR189	Breast (4004199)	Breast (4004199)			
AR190	Breast (4004399)	Breast (4004399)			,
AR191	Breast (4004943B7)	Breast (4004943B7)			
AR192	Breast (4005570B1)	Breast (4005570B1)			
AR193	Breast Cancer	Breast Cancer			-
AR194	(4004127A30) Breast Cancer	(4004127A30) Breast Cancer			
	(400443A21) Breast Cancer	(400443A21)			
AR195	(4004643A2)	Breast Cancer (4004643A2)			
AR196	Breast Cancer (4004710A7)	Breast Cancer (4004710A7)			
AR197	Breast Cancer (4004943A21)	Breast Cancer (4004943A21)			
AR198	Breast Cancer (400553A2)	Breast Cancer (400553A2)			
AR199	Breast Cancer (9805C046R)	Breast Cancer (9805C046R)			
AR200	Breast Cancer (9806C012R)	Breast Cancer (9806C012R)			
AR201	Breast Cancer (ODQ 45913)	Breast Cancer (ODQ 45913)			
AR202	Breast Cancer (ODQ45913)	Breast Cancer (ODQ45913)			
AR203	Breast Cancer (ODQ4591B)	Breast Cancer (ODQ4591B)			
AR204	Colon Cancer (15663)	Colon Cancer	· · · · · · · · · · · · · · · · · · ·		
	* * * * * * * * * * * * * * * * * * * *		 		

		(15662)		F	 	<u> </u>
		(15663)			ļ	
AR205	Colon Cancer	Colon Cancer				
	(4005144A4)	(4005144A4)			ļ	
AR206	Colon Cancer	Colon Cancer			j	
	(4005413A4)	(4005413A4)				
AR207	Colon Cancer	Colon Cancer			l .	
	(4005570B1)	(4005570B1)				
AR208	Control RNA #1	Control RNA #1				
AR209	Control RNA #2	Control RNA #2				
AR210	Cultured Preadipocyte	Cultured				
ARZIO	(blue)	Preadipocyte				1
+	(blue)	(blue)				
AR211	Cultured Preadipocyte	Cultured				-
AKZII	(Red)	Preadipocyte			1	
1	(Red)	(Red)				
AR212	Donor II B-Cells 24hrs	Donor II B-Cells		 		
ARZIZ	Donor II B-Cells 24his	24hrs				
- 1 7010	D HD / DOH					
AR213	Donor II Resting B-Cells	Donor II Resting			1	
15511		B-Cells		 	 	
AR214	H114EP12 10nM Insulin	H114EP12		1		[
		10nM Insulin		 		
AR215	H114EP12 (10nM insulin)	H114EP12				1
		(10nM insulin)		ļ		
AR216	H114EP12 (2.6ug/ul)	H114EP12				
		(2.6ug/ul)		<u> </u>		
AR217	H114EP12 (3.6ug/ul)	H114EP12				
		(3.6ug/ul)				
AR218	HUVEC #1	HUVEC #1				
AR219	HUVEC #2	HUVEC #2				
AR221	L6 undiff.	L6 undiff.				
AR222	L6 Undifferentiated	L6		<u> </u>	1	
ARZZZ	Lo Chamerentiated	Undifferentiated				
AR223	L6P8 + 10nM Insulin	L6P8 + 10nM				
AKZZ	Loro + Tollivi ilisullii	Insulin			1	
4 D224	L6P8 + HS	L6P8 + HS		 	<u> </u>	†
AR224	L6P8 10nM Insulin	L6P8 10nM				
AR225	L6P8 IUnM Insulin					
	**************************************	Insulin	ļ		<u> </u>	
AR226	Liver (00-06-A007B)	Liver (00-06-		1	1	
		A007B)		 	 	
AR227	Liver (96-02-A075)	Liver (96-02-		ļ	İ	
		A075)		<u> </u>	ļ	
AR228	Liver (96-03-A144)	Liver (96-03-				1
		A144)				
AR229	Liver (96-04-A138)	Liver (96-04-				
!		A138)				
AR230	Liver (97-10-A074B)	Liver (97-10-				
į į		A074B)				
AR231	Liver (98-09-A242A)	Liver (98-09-				
	ĺ	A242A)				
AR232	Liver Diabetic (1042)	Liver Diabetic				
1111232	Diver Diabone (10.12)	(1042)				
AR233	Liver Diabetic (41616)	Liver Diabetic			†	
AKZJ	Liver Biabetic (41010)	(41616)			j	
AR234	Liver Diabetic (41955)	Liver Diabetic	1	 	1	
AK234	Liver Diabetic (41933)	(41955)				
1 2005	1 : District (42252D)	Liver Diabetic		 	-	
AR235	Liver Diabetic (42352R)		1			
10000	The District (1995)	(42352R)	<u> </u>	+	+	
AR236	Liver Diabetic (42366)	Liver Diabetic			1	1
		(42366)			-	
AR237	Liver Diabetic (42483)	Liver Diabetic				
	1	(42483)				
			1	1	ı	į.
AR238	Liver Diabetic (42491)	Liver Diabetic			i	· I
		(42491)				
AR238 AR239	Liver Diabetic (42491) Liver Diabetic (99-09-A281A)					

AR241 Lung (27270) Lung (27270)	10040	T			T		
AR242 Lung (2727/Q) Lung (2727/Q)				ļ		ļ	
AR243 Lung Cancer Lung Cancer Lung Cancer AR250 Lung Cancer				ļ			
AR244 Lung Cancer Lung Cancer (4005116.A1) (4005121.A5)							
AR244 Lung Cancer Lung Cancer A005121A5 A005	AR243						
AR245 Lung Cancer (4005121A5)) (4005121A5)) (4005121A5)) (4005121A5)) (4005121A5)) (4005121A5)) (4005121A5)) (4005121A5)) (4005121A5)) (4005121A5)) (4005121A5)) (4005121A5)) (4005121A5)) (4005121A5)) (4005121A5)) (4005121A5)) (4005121A5)) (4005121A5) (4005121A5)) (4005121A5) (400	AR244	Lung Cancer					
AR246 Muscle (99-07-A203B) AR250 Muscle (99-07-A203B) AR260 Muscle (99-07-A203B) AR261 Muscle (99-07-A203B) AR261 Muscle (99-07-A203B) AR261 Muscle (99-07-A203B) AR261 AR262 AR260 Muscle (91-01-A203B) AR260 Muscle (91-01-A203B) AR260 Muscle (91-01-A203B) AR260 AR260 Muscle (91-01-A203B) AR260 AR260 Muscle (91-01-A203B) AR260							
AR246 Lung Cancer	AR245						
AR247 Ammary Gland Ammary Gland AR248 Monocyte (CT) Monocyte (CT) AR249 Monocyte (CT) Monocyte (CT) Monocyte (CT) AR250 Monocytes (CT) Monocytes (CT) AR251 Monocytes (INFG 18 hr) Monocytes (CT) Monocytes (CT) AR252 Monocytes (INFG 18 hr) Monocytes (CT) Monocytes (INFG 18 hr) Monocytes (INFG 18 hr) Monocytes (INFG 18 hr) Monocytes (INFG 8-11	AR246				ļ		
AR248 Monocyte (CT) Monocyte (CT)		(4005340A4)	(4005340A4)				
AR249 Monocyte (OCT) Monocytes (CT)							
AR250 Monocytes (CT) Monocytes (CT)							
AR251 Monocytes (INFG 18 hr) Monocytes (INFG 18 hr)							
AR252 Monocytes (INFG 18hr) Monocytes (INFG 18hr) Monocytes (INFG 18hr) Monocytes (INFG 8-11) Monocytes (INFG 8-11) Monocytes (INFG 8-11) Monocytes (O CT) CT) Monocytes (O CT) Monocytes (O CT) Monocytes (O CT) Monocytes (O CT) Muscle (91-01- A105) Muscle (92-04- A059) Muscle (92-04- A059) Muscle (92-04- A059) Muscle (97-11- A056d) Muscle (97-11- A056d) Muscle (99-06- A210A) Muscle (99-06- A210A) Muscle (99-07- A203B) Muscle (99-07- A203							
AR252 Monocytes (INFG 18hr) Monocytes (INFG 18hr) Monocytes (INFG 18hr) Monocytes (INFG 8-11) Monocytes (INFG 8-11) Monocytes (INFG 8-11) Monocytes (O CT) Monocytes (AKZSI	Monocytes (INFG 18 hr)				1	
ChiPG 18hr Monocytes (INFG 8-11) Monocytes (INFG 8-11) Monocytes (INFG 8-11) Monocytes (INFG 8-11) Monocytes (O CT) CT	AR252	Monocytes (INFG 18hr)				<u> </u>	
AR254 Monocytes (O CT) Monocytes (O CT) CT)			(INFG 18hr)				
AR254 Monocytes (O CT) Monocytes (O CT) CT)	AR253	Monocytes (INFG 8-11)					
AR255 Muscle (91-01-A105) Muscle (91-01-A105) A105) AR256 Muscle (92-04-A059) Muscle (92-04-A059) A059) AR257 Muscle (97-11-A056d) Muscle (99-04-A059) A056d) AR258 Muscle (99-06-A210A) Muscle (99-06-A210A) A1056d) A1	AR254	Monocytes (O CT)	Monocytes (O				
AR256 Muscle (92-04-A059) Muscle (92-04-A059) Muscle (97-11-A056d) Muscle (97-11-A056d) A059)	ADOSS	Mar-1- (01 01 4100)					
AR256 Muscle (92-04-A059) Muscle (92-04-A059) AR257 Muscle (97-11-A056d) Muscle (97-11-A056d) AR258 Muscle (99-06-A210A) Muscle (99-06-A210A) AR259 Muscle (99-07-A203B) Muscle (99-07-A203B) AR260 Muscle (99-7-A203B) Muscle (99-7-A203B) AR261 Muscle Diabetic (42352R) Muscle Diabetic (42352R) AR262 Muscle Diabetic (42352R) Muscle Diabetic (42352R) AR263 NK-19 Control NK-19 Control NK-19 IL Treated 72hrs NK-19 IL Treated 72hrs NK-19 IL Treated 72hrs NK-19 UK Treated 72 hrs. NK-19 UK Treated 72 hrs. NK-19 UK Treated 72 hrs. NK-19 UK Treated 72 hrs. NK-19 UK Treated 72 hrs. Omentum Normal (94-08-B009) Normal (97-01-A039A) Normal (97-01-A039A) Normal (97-04-A114C) Normal (97-04-A114C) Normal (97-06-A117C) Omentum Normal (97-06-A117C) Omentum Normal (97-09-B004C) Omentum Normal (97-09-B004C) Omentum Normal (97-09-B004C) Omentum Normal (97-09-B004C) Omentum Normal (97-09-B004C) Omentum Normal (97-09-B004C) Omentum Normal (97-09-B004C) Ovarian Cancer (17717AID) Ovarian Cancer (17717	AK255	wiuscie (91-01-A105)					
AR257 Muscle (97-11-A056d) Muscle (97-11-A056d) AR258 Muscle (99-06-A210A) Muscle (99-06-A210A) A210A) AR259 Muscle (99-07-A203B) Muscle (99-07-A203B) AR260 Muscle (99-7-A203B) Muscle (99-7-A203B) AR261 Muscle Diabetic (42352R) Muscle Diabetic (42352R) Muscle Diabetic (42352R) AR262 Muscle Diabetic (42366) Muscle Diabetic (42366) AR263 NK-19 Control NK-19 Control NK-19 IL Treated 72hrs NK-19 IL Treated 72hrs NK-19 IL Treated 72hrs NK-19 IL Treated 72hrs NK-19 UK Treated 72 hrs. NK-19 UK Treated 72 hrs. Omentum Normal (94-08-B009) AR266 Omentum Normal (97-01-A039A) Omentum Normal (97-01-A039A) Omentum Normal (97-04-A114C) Omentum Normal (97-04-A114C) Omentum Normal (97-06-A117C) Omentum Normal (97-06-A117C) Omentum Normal (97-09-B004C) Omentum Normal (97-09-B004C) Ovarian Cancer (17717AID) Ovarian Cancer (AR256	Muscle (92-04-A059)					
AR258 Muscle (99-06-A210A) Muscle (99-06-A210A) Muscle (99-06-A210A) AR259 Muscle (99-07-A203B) Muscle (99-07-A203B) AR260 Muscle (99-7-A203B) Muscle (99-7-A203B) AR261 Muscle Diabetic (42352R) Muscle Diabetic (42352R) AR262 Muscle Diabetic (42366) Muscle Diabetic (42352R) AR263 NK-19 Control NK-19 Control AR264 NK-19 IL Treated 72hrs NK-19 IL Treated 72hrs AR265 NK-19 UK Treated 72 hrs. AR266 Omentum Normal (94-08-B009) AR267 Omentum Normal (97-01-A039A) AR268 Omentum Normal (97-04-A114C) AR269 Omentum Normal (97-06-A117C) AR270 Omentum Normal (97-09-B004C) AR271 Ovarian Cancer Ovarian Cancer (17717AID) AR272 Ovarian Cancer Ovarian Cancer Ovarian Cancer (17717AID) AR272 Ovarian Cancer Ovarian Cancer Ovarian Cancer	AR257	Muscle (97-11-A056d)					
AR259 Muscle (99-07-A203B) Muscle (99-07-A203B) AR260 Muscle (99-7-A203B) Muscle (99-7-A203B) AR261 Muscle Diabetic (42352R) Muscle Diabetic (42352R) Muscle Diabetic (42352R) AR262 Muscle Diabetic (42366) Muscle Diabetic (42366) AR263 NK-19 Control NK-19 Control NK-19 UK Treated 72 hrs. NK-19 IL Treated 72 hrs. NK-19 UK Treated 72 hrs. NK-19 UK Treated 72 hrs. Omentum Normal (94-08-B009) Normal (94-08-B009) Normal (97-01-A039A) Normal (97-01-A039A) Omentum Normal (97-04-A114C) Normal (97-04-A114C) Normal (97-06-A117C) Omentum Normal (97-06-A117C) Omentum Normal (97-06-A117C) Omentum Normal (97-06-A117C) Omentum Normal (97-09-B004C) Omentum Normal (97-09-B004C) Omentum Normal (97-09-B004C) Omentum Normal (97-09-B004C) Ovarian Cancer (17717AID) (17717AID) (17717AID) AR272 Ovarian Cancer			A056d)				
AR259 Muscle (99-07-A203B) Muscle (99-07-A203B) AR260 Muscle (99-7-A203B) Muscle (99-7-A203B) AR261 Muscle Diabetic (42352R) Muscle Diabetic (42352R) AR262 Muscle Diabetic (42366) Muscle Diabetic (42366) AR263 NK-19 Control NK-19 Control NK-19 IL Treated 72hrs AR264 NK-19 IL Treated 72hrs. AR265 NK-19 UK Treated 72 hrs. AR266 Omentum Normal (94-08-B009) AR267 Omentum Normal (97-01-A039A) AR268 Omentum Normal (97-04-A114C) AR269 Omentum Normal (97-06-A117C) AR270 Omentum Normal (97-09-B004C) AR271 Ovarian Cancer (17717AID) AR272 Ovarian Cancer Ovarian Cancer	AR258	Muscle (99-06-A210A)					
AR260 Muscle (99-7-A203B) Muscle (99-7-A203B) AR261 Muscle Diabetic (42352R) Muscle Diabetic (42352R) AR262 Muscle Diabetic (42366) Muscle Diabetic (42366) AR263 NK-19 Control NK-19 Control AR264 NK-19 IL Treated 72hrs NK-19 IL Treated 72hrs AR265 NK-19 UK Treated 72 hrs. AR266 Omentum Normal (94-08-B009) AR267 Omentum Normal (97-01-A039A) AR268 Omentum Normal (97-04-A114C) AR269 Omentum Normal (97-06-A117C) AR270 Omentum Normal (97-09-B004C) AR271 Ovarian Cancer (17717AID) AR272 Ovarian Cancer Ovarian Cancer	AR259	Muscle (99-07-A203R)					
AR261 Muscle Diabetic (42352R) Muscle Diabetic (42352R) AR262 Muscle Diabetic (42366) Muscle Diabetic (42366) AR263 NK-19 Control NK-19 Control AR264 NK-19 IL Treated 72hrs Treated 72hrs AR265 NK-19 UK Treated 72 hrs. AR266 Omentum Normal (94-08-B009) AR267 Omentum Normal (97-01-A039A) AR268 Omentum Normal (97-04-A114C) AR269 Omentum Normal (97-06-A117C) AR270 Omentum Normal (97-09-B004C) AR271 Ovarian Cancer (17717AID) AR272 Ovarian Cancer Ovarian Cancer Ovarian Cancer Ovarian Cancer Ovarian Cancer Ovarian Cancer Ovarian Cancer Ovarian Cancer Ovarian Cancer Ovarian Cancer Ovarian Cancer Ovarian Cancer Ovarian Cancer Ovarian Cancer	11(23)	Wascie (77-07-A203B)					
AR262 Muscle Diabetic (42366) Muscle Diabetic (42366) Muscle Diabetic (42366) AR263 NK-19 Control NK-19 Control AR264 NK-19 IL Treated 72hrs NK-19 IL Treated 72hrs NK-19 UK Treated 72hrs AR265 NK-19 UK Treated 72 hrs. NK-19 UK Treated 72 hrs. AR266 Omentum Normal (94-08-	AR260	Muscle (99-7-A203B)					
AR262 Muscle Diabetic (42366) AR263 NK-19 Control AR264 NK-19 IL Treated 72hrs AR265 NK-19 UK Treated 72 hrs. AR266 Omentum Normal (94-08-B009) AR267 Omentum Normal (97-01-A039A) AR268 Omentum Normal (97-04-A114C) AR269 Omentum Normal (97-06-A117C) AR260 Omentum Normal (97-09-B004C) AR270 Omentum Normal (97-09-B004C) AR271 Ovarian Cancer (17717AID) AR272 Ovarian Cancer ONK-19 UK Treated 72 hrs. Omentum NoK-19 UK Treated 72 hrs. Omentum Normal (94-08-B009) Omentum Normal (94-08-B009) Omentum Normal (97-01-A039A) Omentum Normal (97-04-A114C) Omentum Normal (97-06-A117C) Omentum Normal (97-09-B004C) Ovarian Cancer (17717AID) AR272 Ovarian Cancer Ovarian Cancer Ovarian Cancer	AR261	Muscle Diabetic (42352R)					
AR263 NK-19 Control NK-19 Control RR264 NK-19 IL Treated 72hrs NK-19 IL Treated 72hrs NK-19 UK Treated 72 hrs. 039A) Normal (97-04-A114C) Normal (97-04-A114C) Normal (97-04-A114C) Normal (97-06-A117C) Omentum Normal (97-06-A117C) Omentum Normal (97-09-B004C) Omentum Normal (97-09-B004C) Ovarian Cancer (17717AID) (17717AID) AR272 Ovarian Cancer Ovarian Cance	AR262	Muscle Diabetic (42366)	Muscle Diabetic				
AR264 NK-19 IL Treated 72hrs AR265 NK-19 UK Treated 72 hrs. AR266 Omentum Normal (94-08-B009) AR267 Omentum Normal (97-01-A039A) AR268 Omentum Normal (97-04-A114C) AR269 Omentum Normal (97-06-A117C) AR270 Omentum Normal (97-09-B004C) AR271 Ovarian Cancer (17717AID) AR272 Ovarian Cancer Ovarian Cancer	AR263	NK-19 Control					
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B004C) Normal (97-09- B004C)	AR270	Omentum Normal (97-09-					
AR271 Ovarian Cancer (17717AID) Ovarian Cancer (17717AID) AR272 Ovarian Cancer Ovarian Cancer Ovarian Cancer	į		Normal (97-09-				
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AR272 Ovarian Cancer Ovarian Cancer	AR271						
	AR272	·					
		(9905C023RC)	(9905C023RC)		ļ		
AR273 Ovarian Cancer Ovarian Cancer	AR273		Ovarian Cancer				
(9905C032RC) (9905C032RC)		(9905C032RC)	(9905C032RC)				

AR274	Ovary (9508G045)	Ovary (9508G045)				
AR275	Ovary (9701G208)	Ovary (9701G208)				
AR276	Ovary 9806G005	Ovary 9806G005	· · · · · · · · · · · · · · · · · · ·			
AR277	Pancreas	Pancreas	<u> </u>	· · · · · · · · · · · · · · · · · · ·		
AR278	Placebo	Placebo		- 	· · · · · · · · · · · · · · · · · · ·	
AR279	rIL2 Control	rIL2 Control	·	 	 	
AR280	RSS288L	RSS288L		-		
AR281	RSS288LC	RSS288LC				
AR282	Salivary Gland	Salivary Gland				
AR283	Skeletal Muscle	Skeletal Muscle	 	 		
AR284	Skeletal Muscle (91-01-	Skeletal Muscle		 	 	ļ
	A105)	(91-01-A105)				
AR285	Skeletal Muscle (42180)	Skeletal Muscle (42180)				
AR286	Skeletal Muscle (42386)	Skeletal Muscle (42386)				
AR287	Skeletal Muscle (42461)	Skeletal Muscle (42461)				
AR288	Skeletal Muscle (91-01-A105)	Skeletal Muscle (91-01-A105)				
AR289	Skeletal Muscle (92-04-A059)	Skeletal Muscle				
AR290	Skeletal Muscle (96-08-	(92-04-A059) Skeletal Muscle				
ABOOL	A171)	(96-08-A171)			ļ	
AR291	Skeletal Muscle (97-07-	Skeletal Muscle	•	l .	1	
1.000	A190A)	(97-07-A190A)			<u> </u>	
AR292	Skeletal Muscle Diabetic	Skeletal Muscle		İ	į	
AR293	(42352)	Diabetic (42352)			<u> </u>	
	Skeletal Muscle Diabetic (42366)	Skeletal Muscle Diabetic (42366)				
AR294	Skeletal Muscle Diabetic (42395)	Skeletal Muscle Diabetic (42395)				
AR295	Skeletal Muscle Diabetic (42483)	Skeletal Muscle Diabetic (42483)				
AR296	Skeletal Muscle Diabetic	Skeletal Muscle		ļ	ļ	
	(42491)	Diabetic (42491)		<u> </u>		
AR297	Skeletal Muscle Diabetic 42352	Skeletal Muscle Diabetic 42352				
AR298	Skeletal Musle (42461)	Skeletal Musle (42461)				
AR299	Small Intestine	Small Intestine				
AR300	Stomach	Stomach			1	
AR301	T-Cell + HDPBQ71.fc	T-Cell +				
	1449 16hrs	HDPBQ71.fc 1449 16hrs				
AR302	T-Cell + HDPBQ71.fc	T-Cell +			 	
111002	1449 6hrs	HDPBQ71.fc				
A D 202	T Call , H 2 1Cl	1449 6hrs		ļ	ļ	
AR303	T-Cell + IL2 16hrs	T-Cell + IL2 16hrs				
AR304	T-Cell + IL2 6hrs	T-Cell + IL2 6hrs				
AR306	T-Cell Untreated 16hrs	T-Cell Untreated 16hrs				
AR307	T-Cell Untreated 6hrs	T-Cell Untreated 6hrs				
AR308	T-Cells 24 hours	T-Cells 24 hours				
AR309	T-Cells 24 hrs	T-Cells 24 hrs			 -	
AR310	T-Cells 24 hrs.	T-Cells 24 hrs.			 	
AR311	T-Cells 24hrs	T-Cells 24 hrs				
AR311	T-Cells 4 days	T-Cells 4 days				
AR313	Thymus	Thymus				
AR314	TRE	TRE				
		IIL		·	l	

AR315	TREC	TREC	Υ	<u></u>		
AR315 AR316	Virtual Mixture	Virtual Mixture				
H0002	Human Adult Heart	Human Adult Heart	Heart			Uni-ZAP XR
H0003	Human Adult Liver	Human Adult Liver	Liver		1	Uni-ZAP XR
H0004	Human Adult Spleen	Human Adult Spleen	Spleen			Uni-ZAP XR
H0008	Whole 6 Week Old Embryo	Spicen				Uni-ZAP XR
H0009	Human Fetal Brain				1	Uni-ZAP XR
H0011	Human Fetal Kidney	Human Fetal Kidney	Kidney			Uni-ZAP XR
H0012	Human Fetal Kidney	Human Fetal Kidney	Kidney			Uni-ZAP XR
H0013	Human 8 Week Whole Embryo	Human 8 Week Old Embryo	Embryo			Uni-ZAP XR
H0014	Human Gall Bladder	Human Gall Bladder	Gall Bladder			Uni-ZAP XR
H0015	Human Gall Bladder, fraction II	Human Gall Bladder	Gall Bladder			Uni-ZAP XR
H0018	Human Greater Omentum, fII remake	Human Greater Omentum	peritoneum			Uni-ZAP XR
H0019	Human Fetal Heart	Human Fetal Heart	Heart			pBluescript
H0022	Jurkat Cells	Jurkat T-Cell Line				Lambda ZAP II
H0023	Human Fetal Lung					Uni-ZAP XR
H0024	Human Fetal Lung III	Human Fetal Lung	Lung			Uni-ZAP XR
H0025	Human Adult Lymph Node	Human Adult Lymph Node	Lymph Node			Lambda ZAP II
H0026	Namalwa Cells	Namalwa B-Cell Line, EBV immortalized				Lambda ZAP II
H0028	Human Old Ovary	Human Old Ovary	Ovary			pBluescript
H0029	Human Pancreas	Human Pancreas	Pancreas		<u></u>	Uni-ZAP XR
H0030	Human Placenta					Uni-ZAP XR
H0031	Human Placenta	Human Placenta	Placenta		1	Uni-ZAP XR
H0032	Human Prostate	Human Prostate	Prostate			Uni-ZAP XR
H0033	Human Pituitary	Human Pituitary				Uni-ZAP XR
H0035	Human Salivary Gland	Human Salivary Gland	Salivary gland			Uni-ZAP XR
H0036	Human Adult Small Intestine	Human Adult Small Intestine	Small Int.			Uni-ZAP XR
H0037	Human Adult Small Intestine	Human Adult Small Intestine	Small Int.			pBluescript
H0038	Human Testes	Human Testes	Testis			Uni-ZAP XR
H0039	Human Pancreas Tumor	Human Pancreas Tumor	Pancreas		disease	Uni-ZAP XR
H0040	Human Testes Tumor	Human Testes Tumor	Testis		disease	Uni-ZAP XR
H0041	Human Fetal Bone	Human Fetal Bone	Bone			Uni-ZAP XR
H0042	Human Adult Pulmonary	Human Adult Pulmonary	Lung			Uni-ZAP XR
H0044	Human Cornea	Human Cornea	eye			Uni-ZAP XR
H0046	Human Endometrial Tumor	Human Endometrial Tumor	Uterus		disease	Uni-ZAP XR
H0047	Human Fetal Liver	Human Fetal Liver	Liver			Uni-ZAP XR
H0049	Human Fetal Kidney	Human Fetal Kidney	Kidney			Uni-ZAP XR

H0050	Human Fetal Heart	Human Fetal	Heart			Uni-ZAP XR
H0051	Human Hippocampus	Heart Human	Brain			Uni-ZAP XR
H0052	Human Cerebellum	Hippocampus Human	Brain			Uni-ZAP XR
		Cerebellum				
H0053	Human Adult Kidney	Human Adult Kidney	Kidney			Uni-ZAP XR
H0056	Human Umbilical Vein, Endo. remake	Human Umbilical Vein Endothelial Cells	Umbilical vein			Uni-ZAP XR
H0057	Human Fetal Spleen	Zincomona com				Uni-ZAP XR
H0058	Human Thymus Tumor	Human Thymus Tumor	Thymus		disease	Lambda ZAP II
H0059	Human Uterine Cancer	Human Uterine Cancer	Uterus		disease	Lambda ZAP II
H0060	Human Macrophage	Human Macrophage	Blood	Cell Line		pBluescript
H0061	Human Macrophage	Human Macrophage	Blood	Cell Line		pBluescript
H0063	Human Thymus	Human Thymus	Thymus			Uni-ZAP XR
H0064	Human Right Hemisphere of Brain	Human Brain, right hemisphere	Brain			Uni-ZAP XR
H0068	Human Skin Tumor	Human Skin Tumor	Skin		disease	Uni-ZAP XR
H0069	Human Activated T-Cells	Activated T- Cells	Blood	Cell Line		Uni-ZAP XR
H0070	Human Pancreas	Human Pancreas	Pancreas			Uni-ZAP XR
H0071	Human Infant Adrenal Gland	Human Infant Adrenal Gland	Adrenal gland			Uni-ZAP XR
H0075	Human Activated T-Cells (II)	Activated T- Cells	Blood	Cell Line		Uni-ZAP XR
H0081	Human Fetal Epithelium (Skin)	Human Fetal Skin	Skin			Uni-ZAP XR
H0082	Human Fetal Muscle	Human Fetal Muscle	Sk Muscle			Uni-ZAP XR
H0083	HUMAN JURKAT MEMBRANE BOUND POLYSOMES	Jurkat Cells				Uni-ZAP XR
H0085	Human Colon	Human Colon				Lambda ZAP II
H0086	Human epithelioid sarcoma	Epithelioid Sarcoma, muscle	Sk Muscle		disease	Uni-ZAP XR
H0087	Human Thymus	Human Thymus				pBluescript
H0090	Human T-Cell Lymphoma	T-Cell Lymphoma	T-Cell		disease	Uni-ZAP XR
H0093	Human Greater Omentum Tumor	Human Greater Omentum	peritoneum		disease	Uni-ZAP XR
H0095	Human Greater Omentum, RNA Remake	Human Greater Omentum	peritoneum			Uni-ZAP XR
H0097	Human Adult Heart, subtracted	Human Adult Heart	Heart			pBluescript
H0098	Human Adult Liver, subtracted	Human Adult Liver	Liver			Uni-ZAP XR
H0099	Human Lung Cancer, subtracted	Human Lung Cancer	Lung			pBluescript
H0100	Human Whole Six Week Old Embryo	Human Whole Six Week Old Embryo	Embryo			Uni-ZAP XR
H0101	Human 7 Weeks Old Embryo, subtracted	Human Whole 7 Week Old Embryo	Embryo			Lambda ZAP II
H0102	Human Whole 6 Week Old Embryo (II), subt	Human Whole Six Week Old Embryo	Embryo			pBluescript
H0105	Human Fetal Heart,	Human Fetal	Heart			pBluescript

	subtracted	Heart		1		
H0107	Human Infant Adrenal Gland, subtracted	Human Infant Adrenal Gland	Adrenal gland			pBluescript
H0108	Human Adult Lymph Node, subtracted	Human Adult Lymph Node	Lymph Node			Uni-ZAP XR
H0109	Human Macrophage, subtracted	Macrophage	Blood	Cell Line		pBluescript
H0111	Human Placenta, subtracted	Human Placenta	Placenta			pBluescript
H0116	Human Thymus Tumor, subtracted	Human Thymus Tumor	Thymus			pBluescript
H0117	Human Uterine Cancer, subtracted	Human Uterine Cancer	Uterus			pBluescript
H0119	Human Pediatric Kidney	Human Pediatric Kidney	Kidney			Uni-ZAP XR
H0121	Human Cornea, subtracted	Human Cornea	eye			Uni-ZAP XR
H0122	Human Adult Skeletal Muscle	Human Skeletal Muscle	Sk Muscle			Uni-ZAP XR
H0123	Human Fetal Dura Mater	Human Fetal Dura Mater	Brain			Uni-ZAP XR
H0124	Human Rhabdomyosarcoma	Human Rhabdomyosarco ma	Sk Muscle		disease	Uni-ZAP XR
H0125	Cem cells cyclohexamide treated	Cyclohexamide Treated Cem, Jurkat, Raji, and Supt	Blood	Cell Line		Uni-ZAP XR
H0129	Jurkat cells, thiouridine activated, fract II	Jurkat Cells				Uni-ZAP XR
H0130	LNCAP untreated	LNCAP Cell Line	Prostate	Cell Line		Uni-ZAP XR
H0131	LNCAP + 0.3nM R1881	LNCAP Cell Line	Prostate	Cell Line		Uni-ZAP XR
H0132	LNCAP + 30nM R1881	LNCAP Cell Line	Prostate	Cell Line		Uni-ZAP XR
H0134	Raji Cells, cyclohexamide treated	Cyclohexamide Treated Cem, Jurkat, Raji, and Supt	Blood	Cell Line		Uni-ZAP XR
H0135	Human Synovial Sarcoma	Human Synovial Sarcoma	Synovium			Uni-ZAP XR
H0136	Supt Cells, cyclohexamide treated	Cyclohexamide Treated Cem, Jurkat, Raji, and Supt	Blood	Cell Line		Uni-ZAP XR
H0140	Activated T-Cells, 8 hrs.	Activated T- Cells	Blood	Cell Line		Uni-ZAP XR
H0141	Activated T-Cells, 12 hrs.	Activated T- Cells	Blood	Cell Line		Uni-ZAP XR
H0142	MCF7 Cell Line	MCF7 Cell line	Breast	Cell Line		Uni-ZAP XR
H0144	Nine Week Old Early Stage Human	9 Wk Old Early Stage Human	Embryo			Uni-ZAP XR
H0147	Human Adult Liver	Human Adult Liver	Liver			Uni-ZAP XR
H0149	7 Week Old Early Stage Human, subtracted	Human Whole 7 Week Old Embryo	Embryo			Uni-ZAP XR
H0150	Human Epididymus	Epididymis	Testis			Uni-ZAP XR
H0151	Early Stage Human Liver	Human Fetal Liver	Liver			Uni-ZAP XR
H0154	Human Fibrosarcoma	Human Skin Fibrosarcoma	Skin		disease	Uni-ZAP XR
H0155	Human Thymus, subtracted	Human Thymus Tumor	Thymus			pBluescript
H0156	Human Adrenal Gland	Human Adrenal	Adrenal	1	disease	Uni-ZAP XR

	Tumor	Gland Tumor	Gland	<u> </u>		
H0157	Activated T-Cells, 0 hrs,	Activated T-	Blood	Cell Line		Uni-ZAP XR
	ligation 2	Cells	J.00 u	Con Eme		OIII-ZAI AK
H0159	Activated T-Cells, 8 hrs., ligation 2	Activated T- Cells	Blood	Cell Line		Uni-ZAP XR
H0161	Activated T-Cells, 24 hrs., ligation 2	Activated T- Cells	Blood	Cell Line		Uni-ZAP XR
H0163	Human Synovium	Human Synovium	Synovium			Uni-ZAP XR
H0165	Human Prostate Cancer, Stage B2	Human Prostate Cancer, stage B2	Prostate		disease	Uni-ZAP XR
H0166	Human Prostate Cancer, Stage B2 fraction	Human Prostate Cancer, stage B2	Prostate		disease	Uni-ZAP XR
H0167	Activated T-Cells, 24 hrs.	Activated T- Cells	Blood	Cell Line		Uni-ZAP XR
H0169	Human Prostate Cancer, Stage C fraction	Human Prostate Cancer, stage C	Prostate		disease	Uni-ZAP XR
H0170	12 Week Old Early Stage Human	Twelve Week Old Early Stage Human	Embryo			Uni-ZAP XR
H0171	12 Week Old Early Stage Human, II	Twelve Week Old Early Stage Human	Embryo			Uni-ZAP XR
H0172	Human Fetal Brain, random primed	Human Fetal Brain	Brain			Lambda ZAP II
H0173	Human Cardiomyopathy, RNA remake	Human Cardiomyopathy	Heart		disease	Uni-ZAP XR
H0175	H. Adult Spleen, ziplox			·		pSport1
H0177	CAMA1Ee Cell Line	CAMA1Ee Cell Line	Breast	Cell Line		Uni-ZAP XR
H0178	Human Fetal Brain	Human Fetal Brain	Brain			Uni-ZAP XR
H0179	Human Neutrophil	Human Neutrophil	Blood	Cell Line		Uni-ZAP XR
H0181	Human Primary Breast Cancer	Human Primary Breast Cancer	Breast		disease	Uni-ZAP XR
H0182	Human Primary Breast Cancer	Human Primary Breast Cancer	Breast		disease	Uni-ZAP XR
H0183	Human Colon Cancer	Human Colon Cancer	Colon		disease	Uni-ZAP XR
H0187	Resting T-Cell	T-Cells	Blood	Cell Line		Lambda ZAP II
H0188	Human Normal Breast	Human Normal Breast	Breast			Uni-ZAP XR
H0190	Human Activated Macrophage (LPS)	Human Macrophage/Mo nocytes	Blood	Cell Line		Uni-ZAP XR
H0191	Human Activated Macrophage (LPS), thiour	Human Macrophage/Mo nocytes	Blood	Cell Line		Uni-ZAP XR
H0194	Human Cerebellum, subtracted	Human Cerebellum	Brain			pBluescript
H0196	Human Cardiomyopathy, subtracted	Human Cardiomyopathy	Heart			Uni-ZAP XR
H0197	Human Fetal Liver, subtracted	Human Fetal Liver	Liver			Uni-ZAP XR
H0199	Human Fetal Liver, subtracted, neg clone	Human Fetal Liver	Liver			Uni-ZAP XR
H0200	Human Greater Omentum, fract II remake,	Human Greater Omentum	peritoneum			Uni-ZAP XR
H0201	Human Hippocampus, subtracted	Human Hippocampus	Brain			pBluescript
H0202	Jurkat Cells, cyclohexamide treated, subtraction	Cyclohexamide Treated Cem, Jurkat, Raji, and Supt	Blood	Cell Line		Uni-ZAP XR

H0204	Human Colon Cancer, subtracted	Human Colon Cancer	Colon			pBluescript
H0205	Human Colon Cancer, differential	Human Colon Cancer	Colon			pBluescript
H0207	LNCAP, differential expression	LNCAP Cell Line	Prostate	Cell Line		pBluescript
H0208	Early Stage Human Lung, subtracted	Human Fetal Lung	Lung			pBluescript
H0209	Human Cerebellum, differentially expressed	Human Cerebellum	Brain			Uni-ZAP XR
H0211	Human Prostate, differential expression	Human Prostate	Prostate			pBluescript
H0212	Human Prostate, subtracted	Human Prostate	Prostate			pBluescript
H0213	Human Pituitary, subtracted	Human Pituitary				Uni-ZAP XR
H0214	Raji cells, cyclohexamide treated, subtracted	Cyclohexamide Treated Cem, Jurkat, Raji, and Supt	Blood	Cell Line		pBluescript
H0215	Raji cells, cyclohexamide treated, differentially expressed	Cyclohexamide Treated Cem, Jurkat, Raji, and Supt	Blood	Cell Line		pBluescript
H0216	Supt cells, cyclohexamide treated, subtracted	Cyclohexamide Treated Cem, Jurkat, Raji, and Supt	Blood	Cell Line		pBluescript
H0217	Supt cells, cyclohexamide treated, differentially expressed	Cyclohexamide Treated Cem, Jurkat, Raji, and Supt	Blood	Cell Line		pBluescript
H0218	Activated T-Cells, 0hrs, subtracted	Activated T- Cells	Blood	Cell Line		Uni-ZAP XR
H0219	Activated T-Cells, 0hrs, differentially expressed	Activated T- Cells	Blood	Cell Line		Uni-ZAP XR
H0220	Activated T-Cells, 4 hrs, subtracted	Activated T- Cells	Blood	Cell Line		Uni-ZAP XR
H0222	Activated T-Cells, 8 hrs, subtracted	Activated T- Cells	Blood	Cell Line		Uni-ZAP XR
H0224	Activated T-Cells, 12 hrs, subtracted	Activated T- Cells	Blood	Cell Line		Uni-ZAP XR
H0225	Activated T-Cells, 12hrs, differentially expressed	Activated T- Cells	Blood	Cell Line		Uni-ZAP XR
H0228	C7MCF7 cell line, estrogen treated	C7MCF7 Cell Line, estrogen treated	Breast	Cell Line		Uni-ZAP XR
H0229	Early Stage Human Brain, random primed	Early Stage Human Brain	Brain			Lambda ZAP II
H0230	Human Cardiomyopathy, diff exp	Human Cardiomyopathy	Heart		disease	Uni-ZAP XR
H0231	Human Colon, subtraction	Human Colon				pBluescript
H0232	Human Colon, differential expression	Human Colon				pBluescript
H0234	human colon cancer, metastatic to liver, differentially expressed	Human Colon Cancer, metasticized to liver	Liver			pBluescript
H0235	Human colon cancer, metaticized to liver, subtraction	Human Colon Cancer, metasticized to liver	Liver			pBluescript
H0238	Human Myometrium Leiomyoma	Human Myometrium Leiomyoma	Uterus		disease	Uni-ZAP XR

H0239	Human Kidney Tumor	Human Kidney	Vidnov	T	1 4:	I II ZADVO
110239	Truman Kidney Tumor	Tumor	Kidney		disease	Uni-ZAP XR
H0241	C7MCF7 cell line, estrogen treated, subtraction	C7MCF7 Cell Line, estrogen treated	Breast	Cell Line		Uni-ZAP XR
H0242	Human Fetal Heart, Differential (Fetal- Specific)	Human Fetal Heart	Heart			pBluescript
H0244	Human 8 Week Whole Embryo, subtracted	Human 8 Week Old Embryo	Embryo			Uni-ZAP XR
H0246	Human Fetal Liver- Enzyme subtraction	Human Fetal Liver	Liver			Uni-ZAP XR
H0247	Human Membrane Bound Polysomes- Enzyme Subtraction	Human Membrane Bound Polysomes	Blood	Cell Line	i	Uni-ZAP XR
H0250	Human Activated Monocytes	Human Monocytes				Uni-ZAP XR
H0251	Human Chondrosarcoma	Human Chondrosarcoma	Cartilage		disease	Uni-ZAP XR
H0252	Human Osteosarcoma	Human Osteosarcoma	Bone		disease	Uni-ZAP XR
H0253	Human adult testis, large inserts	Human Adult Testis	Testis			Uni-ZAP XR
H0254	Breast Lymph node cDNA library	Breast Lymph Node	Lymph Node			Uni-ZAP XR
H0255	breast lymph node CDNA library	Breast Lymph Node	Lymph Node			Lambda ZAP II
H0256	HL-60, unstimulated	Human HL-60 Cells, unstimulated	Blood	Cell Line		Uni-ZAP XR
H0257	HL-60, PMA 4H	HL-60 Cells, PMA stimulated 4H	Blood	Cell Line		Uni-ZAP XR
H0261	H. cerebellum, Enzyme subtracted	Human Cerebellum	Brain			Uni-ZAP XR
H0263	human colon cancer	Human Colon Cancer	Colon		disease	Lambda ZAP II
H0264	human tonsils	Human Tonsil	Tonsil			Uni-ZAP XR
H0265	Activated T-Cell (12hs)/Thiouridine labelledEco	T-Cells	Blood	Cell Line		Uni-ZAP XR
H0266	Human Microvascular Endothelial Cells, fract. A	НМЕС	Vein	Cell Line		Lambda ZAP II
H0267	Human Microvascular Endothelial Cells, fract. B	НМЕС	Vein	Cell Line		Lambda ZAP II
H0268	Human Umbilical Vein Endothelial Cells, fract. A	HUVE Cells	Umbilical vein	Cell Line		Lambda ZAP II
H0269	Human Umbilical Vein Endothelial Cells, fract. B	HUVE Cells	Umbilical vein	Cell Line		Lambda ZAP II
H0270	HPAS (human pancreas, subtracted)	Human Pancreas	Pancreas			Uni-ZAP XR
H0271	Human Neutrophil, Activated	Human Neutrophil - Activated	Blood	Cell Line		Uni-ZAP XR
H0272	HUMAN TONSILS, FRACTION 2	Human Tonsil	Tonsil			Uni-ZAP XR
H0274	Human Adult Spleen, fractionII	Human Adult Spleen	Spleen			Uni-ZAP XR
H0275	Human Infant Adrenal Gland, Subtracted	Human Infant Adrenal Gland	Adrenal gland			pBluescript
H0279	K562 cells	K562 Cell line	cell line	Cell Line		ZAP Express
H0280	K562 + PMA (36 hrs)	K562 Cell line	cell line	Cell Line		ZAP Express
H0284	Human OB MG63 control fraction I	Human Osteoblastoma	Bone	Cell Line		Uni-ZAP XR

		MG63 cell line	1			T
H0286	Human OB MG63 treated	Human	Bone	Cell Line	-	Uni-ZAP XR
110200	(10 nM E2) fraction I	Osteoblastoma MG63 cell line	Bonc	Cen Eme		OIII-ZAF AK
H0288	Human OB HOS control	Human	Bone	Cell Line		Uni-ZAP XR
	fraction I	Osteoblastoma	D on .c	Con Eme	ŀ	OIII-ZAI AK
		HOS cell line				
H0290	Human OB HOS treated	Human	Bone	Cell Line		Uni-ZAP XR
	(1 nM E2) fraction I	Osteoblastoma	1 20		l	
	`,	HOS cell line				
H0292	Human OB HOS treated	Human	Bone	Cell Line		Uni-ZAP XR
	(10 nM E2) fraction I	Osteoblastoma	-55			
		HOS cell line	i	ļ		
H0293	WI 38 cells					Uni-ZAP XR
H0294	Amniotic Cells - TNF	Amniotic Cells -	Placenta	Cell Line		Uni-ZAP XR
	induced	TNF induced	110001110	Con Bine		Om Zin AK
H0295	Amniotic Cells - Primary	Amniotic Cells -	Placenta	Cell Line	<u> </u>	Uni-ZAP XR
	Culture	Primary Culture	1	Con Zine		Olli Ziti Ak
H0300	CD34 positive cells (Cord	CD34 Positive	Cord Blood			ZAP Express
	Blood)	Cells	Cold Blood		•	ZAI Expicss
H0305	CD34 positive cells (Cord	CD34 Positive	Cord Blood	†		ZAP Express
	Blood)	Cells	Co.a Diooa			Zen Expicss
H0306	CD34 depleted Buffy Coat	CD34 Depleted	Cord Blood		 	ZAP Express
	(Cord Blood)	Buffy Coat (Cord	Cold Blood			ZAI LAPICSS
	` /	Blood)	ı			
H0309	Human Chronic Synovitis	Synovium,	Synovium		disease	Uni-ZAP XR
		Chronic	by no vium		discase	OM-ZAI AK
		Synovitis/				
		Osteoarthritis				
H0310	human caudate nucleus	Brain	Brain			Uni-ZAP XR
H0313	human pleural cancer	pleural cancer	<u> </u>		disease	pBluescript
H0316	HUMAN STOMACH	Human Stomach	Stomach		uisease	Uni-ZAP XR
H0318	HUMAN B CELL	Human B Cell	Lymph		diagona	
110510	LYMPHOMA	Lymphoma	Node		disease	Uni-ZAP XR
H0320	Human frontal cortex	Human Frontal	Brain			II.: ZADVD
110320	Human Hontai Cortex	Cortex	Drain			Uni-ZAP XR
H0327	human corpus colosum	Human Corpus	Brain			II-: ZADVD
110327	numan corpus colosum	Callosum	brain			Uni-ZAP XR
H0328	human ovarian cancer	Ovarian Cancer	Over		3:	Hai ZAD VD
H0329	Dermatofibrosarcoma	Dermatofibrosarc	Ovary Skin		disease	Uni-ZAP XR
110329	Protuberance	oma Protuberans	SKIN		disease	Uni-ZAP XR
H0331	Hepatocellular Tumor		T :		1.	7 11 5 5
110551	Hepatocential Tumor	Hepatocellular	Liver		disease	Lambda ZAP II
H0333	Hemangiopericytoma	Tumor	D11		.1:	7 11 27 22
110333	Tremangiopericytoma	Hemangiopericyt	Blood		disease	Lambda ZAP II
H0334	Vidney concer	oma Vidnov Compon	vessel			
H0334 H0339	Kidney cancer	Kidney Cancer	Kidney		disease	Uni-ZAP XR
	Duodenum	Duodenum				Uni-ZAP XR
H0340	Corpus Callosum	Corpus				Uni-ZAP XR
1102.41	D M C :: *:	Collosum-93052				
H0341	Bone Marrow Cell Line	Bone Marrow	Bone	Cell Line		Uni-ZAP XR
1100.40	(RS4;11)	Cell Line RS4;11	Marrow			
H0343	stomach cancer (human)	Stomach Cancer			disease	Uni-ZAP XR
1100		- 5383A (human)				
H0344	Adipose tissue (human)	Adipose - 6825A				Uni-ZAP XR
7705 1 -	OVEN.	(human)	-			
H0345	SKIN	Skin - 4000868H	Skin			Uni-ZAP XR
H0346	Brain-medulloblastoma	Brain	Brain		disease	Uni-ZAP XR
		(Medulloblastom				
		a)-9405C006R				
H0349	human adult liver cDNA	Human Adult	Liver			pCMVSport 1
	library	Liver				<u> </u>
H0350	Human Fetal Liver, mixed	Human Fetal	Liver			Uni-ZAP XR
	10014 1	Liver, mixed		İ		
	10 & 14 week					
H0351	Glioblastoma	10&14 Week Glioblastoma				

H0352	wilm"s tumor	Wilm"s Tumor		1	disease	Uni-ZAP XR
H0354	Human Leukocytes	Human Leukocytes	Blood	Cell Line		pCMVSport 1
H0355	Human Liver	Human Liver, normal Adult				pCMVSport 1
H0356	Human Kidney	Human Kidney	Kidney			pCMVSport 1
H0357	H. Normalized Fetal Liver, II	Human Fetal Liver	Liver			Uni-ZAP XR
H0359	KMH2 cell line	KMH2				ZAP Express
H0361	Human rejected kidney	Human Rejected Kidney			disease	pBluescript
H0362	HeLa cell line	HELA CELL LINE				pSport1
H0363	Human Brain Medulla, subtracted	Human Brain Medulla				pBluescript
H0365	Osteoclastoma-normalized B	Human Osteoclastoma			disease	Uni-ZAP XR
H0366	L428 cell line	L428				ZAP Express
Н0369	H. Atrophic Endometrium	Atrophic Endometrium and myometrium				Uni-ZAP XR
Н0370	H. Lymph node breast Cancer	Lymph node with Met. Breast Cancer			disease	Uni-ZAP XR
H0371	Eosinophils- Hypereosinophilia patient	Eosinophils- Hypereosinophili a patient			disease	Uni-ZAP XR
H0372	Human Testes	Human Testes	Testis			pCMVSport 1
H0373	Human Heart	Human Adult Heart	Heart			pCMVSport 1
H0374	Human Brain	Human Brain				pCMVSport 1
H0375	Human Lung	Human Lung				pCMVSport 1
H0376	Human Spleen	Human Adult Spleen	Spleen			pCMVSport 1
H0379	Human Tongue, frac 1	Human Tongue				pSport1
H0380	Human Tongue, frac 2	Human Tongue				pSport1
H0381	Bone Cancer	Bone Cancer			disease	Uni-ZAP XR
H0383	Human Prostate BPH, re- excision	Human Prostate BPH				Uni-ZAP XR
H0385	H. Leukocytes, Kozak	Human Leukocytes	Blood	Cell Line		pCMVSport 1
H0386	Leukocyte and Lung; 4 screens	Human Leukocytes	Blood	Cell Line		pCMVSport 1
H0388	Human Rejected Kidney, 704 re-excision	Human Rejected Kidney			disease	pBluescript
Н0390	Human Amygdala Depression, re-excision	Human Amygdala Depression			disease	pBluescript
H0391	H. Meniingima, M6	Human Meningima	brain			pSport1
H0392	H. Meningima, M1	Human Meningima	brain			pSport1
Н0393	Fetal Liver, subtraction II	Human Fetal Liver	Liver			pBluescript
H0394	A-14 cell line	Redd-Sternberg cell				ZAP Express
H0395	A1-CELL LINE	Redd-Sternberg cell				ZAP Express
H0396	L1 Cell line	Redd-Sternberg cell				ZAP Express
H0399	Human Kidney Cortex, re- rescue	Human Kidney Cortex				Lambda ZAP II
H0400	Human Striatum Depression, re-rescue	Human Brain, Striatum Depression	Brain			Lambda ZAP II

110400	LCD24 L L LD CO C	T				
H0402	CD34 depleted Buffy Coat (Cord Blood), re-excision	CD34 Depleted Buffy Coat (Cord	Cord Blood			ZAP Express
	(Cold Blood), 1c-excision	Blood)	1			
H0403	H. Umbilical Vein	HUVE Cells	Umbilical	Cell Line		Uni-ZAP XR
	Endothelial Cells, IL4 induced		vein			om ZM AK
H0404	H. Umbilical Vein	HUVE Cells	Umbilical	Cell Line		Uni-ZAP XR
	endothelial cells, uninduced		vein	Con Zine		OIII-ZAI AR
H0405	Human Pituitary, subtracted VI	Human Pituitary				pBluescript
H0406	H Amygdala Depression,	Human				Uni-ZAP XR
	subtracted	Amygdala Depression				
H0408	Human kidney Cortex, subtracted	Human Kidney Cortex				pBluescript
H0409	H. Striatum Depression, subtracted	Human Brain, Striatum Depression	Brain			pBluescript
H0411	H Female Bladder, Adult	Human Female Adult Bladder	Bladder			pSport1
H0412	Human umbilical vein	HUVE Cells	Umbilical	Cell Line		pSport1
	endothelial cells, IL-4 induced		vein			.
H0413	Human Umbilical Vein	HUVE Cells	Umbilical	Cell Line		pSport1
	Endothelial Cells, uninduced		vein			
H0414	Ovarian Tumor I, OV5232	Ovarian Tumor, OV5232	Ovary		disease	pSport1
H0415	H. Ovarian Tumor, II, OV5232	Ovarian Tumor, OV5232	Ovary		disease	pCMVSport 2.0
H0416	Human Neutrophils,	Human	Blood	Cell Line		pBluescript
	Activated, re-excision	Neutrophil - Activated				
H0417	Human Pituitary,	Human Pituitary				pBluescript
	subtracted VIII	Trumum Trumum y				politiescript
H0419	Bone Cancer, re-excision	Bone Cancer				Uni-ZAP XR
H0421	Human Bone Marrow, re- excision	Bone Marrow				pBluescript
H0422	T-Cell PHA 16 hrs	T-Cells	Blood	Cell Line		pSport1
H0423	T-Cell PHA 24 hrs	T-Cells	Blood	Cell Line		pSport1
H0424 H0427	Human Pituitary, subt IX	Human Pituitary				pBluescript
H0427	Human Adipose	Human Adipose, left hiplipoma				pSport1
H0428	Human Ovary	Human Ovary Tumor	Ovary			pSport1
H0429	K562 + PMA (36 hrs),re- excision	K562 Cell line	cell line	Cell Line		ZAP Express
H0431	H. Kidney Medulla, re- excision	Kidney medulla	Kidney		- ,	pBluescript
H0432	H. Kidney Pyramid	Kidney pyramids	Kidney			pBluescript
H0433	Human Umbilical Vein	HUVE Cells	Umbilical	Cell Line		pBluescript
	Endothelial cells, frac B, re-excision		vein			r
H0434	Human Brain, striatum, re-excision	Human Brain, Striatum				pBluescript
H0435	Ovarian Tumor 10-3-95	Ovarian Tumor, OV350721	Ovary			pCMVSport 2.0
H0436	Resting T-Cell Library,II	T-Cells	Blood	Cell Line		pSport1
H0437	H Umbilical Vein	HUVE Cells	Umbilical	Cell Line		Lambda ZAP II
	Endothelial Cells, frac A, re-excision		vein		1	
H0438	H. Whole Brain #2, re- excision	Human Whole Brain #2				ZAP Express
H0439	Human Eosinophils	Eosinophils				pBluescript

H0441	H. Kidney Cortex,	Kidney cortex	Kidney		Т	pBluescript
****	subtracted		Triditey			pBluescript
H0443	H. Adipose, subtracted	Human Adipose, left hiplipoma				pSport1
H0444	Spleen metastic melanoma	Spleen, Metastic malignant melanoma	Spleen		disease	pSport1
H0445	Spleen, Chronic lymphocytic leukemia	Human Spleen, CLL	Spleen		disease	pSport1
H0449	CD34+ cell, I	CD34 positive cells				pSport1
H0450	CD34+cells, II	CD34 positive cells				pCMVSport 2.0
H0453	H. Kidney Pyramid, subtracted	Kidney pyramids	Kidney			pBluescript
H0455	H. Striatum Depression, subt	Human Brain, Striatum Depression	Brain			pBluescript
H0456	H Kidney Cortex, subtracted III	Human Kidney Cortex				pBluescript
H0457	Human Eosinophils	Human Eosinophils				pSport1
H0458	CD34+ cell, I, frac II	CD34 positive cells				pSport1
H0459	CD34+cells, II, FRACTION 2	CD34 positive cells				pCMVSport 2.0
H0461	H. Kidney Medulla, subtracted	Kidney medulla	Kidney			pBluescript
H0477	Human Tonsil, Lib 3	Human Tonsil	Tonsil			pSport1
H0478	Salivary Gland, Lib 2	Human Salivary Gland	Salivary gland			pSport1
H0479	Salivary Gland, Lib 3	Human Salivary Gland	Salivary gland			pSport1
H0483	Breast Cancer cell line, MDA 36	Breast Cancer Cell line, MDA 36				pSport1
H0484	Breast Cancer Cell line, angiogenic	Breast Cancer Cell line, Angiogenic, 36T3				pSport1
H0485	Hodgkin"s Lymphoma I	Hodgkin"s Lymphoma I			disease	pCMVSport 2.0
H0486	Hodgkin"s Lymphoma II	Hodgkin"s Lymphoma II			disease	pCMVSport 2.0
H0487	Human Tonsils, lib I	Human Tonsils				pCMVSport 2.0
H0488	Human Tonsils, Lib 2	Human Tonsils				pCMVSport 2.0
H0489	Crohn"s Disease	Ileum	Intestine		disease	pSport1
H0492	HL-60, RA 4h, Subtracted	HL-60 Cells, RA stimulated for 4H	Blood	Cell Line		Uni-ZAP XR
H0493	HL-60, PMA 1d, subtracted	HL-60 Cells, PMA stimulated for 1 day	Blood	Cell Line		Uni-ZAP XR
H0494	Keratinocyte	Keratinocyte				pCMVSport 2.0
H0497	HEL cell line	HEL cell line		HEL 92.1.7		pSport1
H0505	Human Astrocyte	Human Astrocyte				pSport1
H0506	Ulcerative Colitis	Colon	Colon			pSport1
H0509	Liver, Hepatoma	Human Liver, Hepatoma, patient 8	Liver		disease	pCMVSport 3.0
H0510	Human Liver, normal	Human Liver, normal, Patient # 8	Liver			pCMVSport 3.0
H0517 H0518	Nasal polyps	Nasal polyps				pCMVSport 2.0
	pBMC stimulated w/ poly	pBMC				pCMVSport 3.0

	ΙΛC	stimulated with	<u> </u>	Τ	T	<u></u>
		poly I/C				j
H0519	NTERA2, control	NTERA2, Teratocarcinoma cell line				pCMVSport 3.0
H0520	NTERA2 + retinoic acid, 14 days	NTERA2, Teratocarcinoma cell line				pSport1
H0521	Primary Dendritic Cells, lib 1	Primary Dendritic cells				pCMVSport 3.0
H0522	Primary Dendritic cells, frac 2	Primary Dendritic cells				pCMVSport 3.0
H0525	PCR, pBMC I/C treated	pBMC stimulated with poly I/C				PCRII
H0528	Poly[I]/Poly[C] Normal Lung Fibroblasts	Poly[I]/Poly[C] Normal Lung Fibroblasts				pCMVSport 3.0
H0529	Myoloid Progenitor Cell Line	TF-1 Cell Line; Myoloid progenitor cell line				pCMVSport 3.0
H0530	Human Dermal Endothelial Cells,untreated	Human Dermal Endothelial Cells; untreated				pSport1
H0535	Human ovary tumor cell OV350721	Ovarian Tumor, OV350721	Ovary		disease	pSport1
H0538	Merkel Cells	Merkel cells	Lymph node			pSport1
H0539	Pancreas Islet Cell Tumor	Pancreas Islet Cell Tumour	Pancreas		disease	pSport1
H0540	Skin, burned	Skin, leg burned	Skin			pSport1
H0542	T Cell helper I	Helper T cell				pCMVSport 3.0
H0543 H0544	T cell helper II Human endometrial	Helper T cell		ļ		pCMVSport 3.0
110344	stromal cells	Human endometrial stromal cells				pCMVSport 3.0
H0545	Human endometrial stromal cells-treated with progesterone	Human endometrial stromal cells- treated with proge				pCMVSport 3.0
H0546	Human endometrial stromal cells-treated with estradiol	Human endometrial stromal cells- treated with estra				pCMVSport 3.0
H0547	NTERA2 teratocarcinoma cell line+retinoic acid (14 days)	NTERA2, Teratocarcinoma cell line				pSport1
H0549	H. Epididiymus, caput & corpus	Human Epididiymus, caput and corpus				Uni-ZAP XR
H0550	H. Epididiymus, cauda	Human Epididiymus, cauda				Uni-ZAP XR
H0551	Human Thymus Stromal Cells	Human Thymus Stromal Cells				pCMVSport 3.0
H0553	Human Placenta	Human Placenta				pCMVSport 3.0
H0555	Rejected Kidney, lib 4	Human Rejected Kidney	Kidney		disease	pCMVSport 3.0
Н0556	Activated T- cell(12h)/Thiouridine-re- excision	T-Cells	Blood	Cell Line		Uni-ZAP XR
H0559	HL-60, PMA 4H, re- excision	HL-60 Cells, PMA stimulated 4H	Blood	Cell Line		Uni-ZAP XR

H0560	KMH2	12) (110	T			
H0561	L428	KMH2			 	pCMVSport 3.0
H0562	Human Fetal Brain,	L428			1	pCMVSport 3.0
H0302	normalized c5-11-26	Human Fetal				pCMVSport 2.0
H0563	Human Fetal Brain,	Brain	<u> </u>	-		
HUSOS		Human Fetal	ļ	1		pCMVSport 2.0
1105.64	normalized 50021F	Brain	 			
H0564	Human Fetal Brain,	Human Fetal				pCMVSport 2.0
	normalized C5001F	Brain				
H0565	HUman Fetal Brain,	Human Fetal]	1	pCMVSport 2.0
	normalized 100024F	Brain		<u> </u>		1
H0566	Human Fetal	Human Fetal				pCMVSport 2.0
	Brain, normalized c50F	Brain		ľ		1
H0567	Human Fetal Brain,	Human Fetal				pCMVSport 2.0
Į.	normalized A5002F	Brain			1	Para Para
H0569	Human Fetal Brain,	Human Fetal			<u> </u>	pCMVSport 2.0
i i	normalized CO	Brain		1	ļ	point v Sport 2.0
H0570	Human Fetal Brain,	Human Fetal		 	1	pCMVSport 2.0
	normalized C500H	Brain				pelvi v Sport 2.0
H0571	Human Fetal Brain,	Human Fetal		 		-CMVC+20
110371	normalized C500HE	Brain		[pCMVSport 2.0
H0572	Human Fetal Brain,	Human Fetal		<u> </u>	 	-C) (VC 2.0
110372	normalized AC5002	Brain		1		pCMVSport 2.0
H0574	Hepatocellular Tumor; re-		T.		ļ.,	I
10374	excision	Hepatocellular	Liver		disease	Lambda ZAP II
110575		Tumor		ļ		
H0575	Human Adult	Human Adult	Lung			Uni-ZAP XR
110576	Pulmonary;re-excision	Pulmonary				
H0576	Resting T-Cell; re-	T-Cells	Blood	Cell Line		Lambda ZAP II
	excision					
H0580	Dendritic cells, pooled	Pooled dendritic				pCMVSport 3.0
		cells			1	
H0581	Human Bone Marrow,	Human Bone	Bone			pCMVSport 3.0
	treated	Marrow	Marrow			1
H0583	B Cell lymphoma	B Cell	B Cell		disease	pCMVSport 3.0
		Lymphoma				
H0584	Activated T-cells, 24	Activated T-	Blood	Cell Line		Uni-ZAP XR
	hrs,re-excision	Cells				om En na
H0585	Activated T-Cells,12	Activated T-	Blood	Cell Line		Uni-ZAP XR
1	hrs,re-excision	Cells	2.00	l con Bine		Om-ZAI AK
H0586	Healing groin wound, 6.5	healing groin	groin		disease	pCMVSport 3.0
	hours post incision	wound, 6.5 hours	grom.		discase	pen v spon 3.0
j	P	post incision - 2/			ļ	
H0587	Healing groin wound; 7.5	Groin-2/19/97	groin		disease	pCMVSport 3.0
	hours post incision	Grom 2/19/97	grom		uisease	pew v sport 3.0
H0589	CD34 positive cells (cord	CD34 Positive	Cord Blood			7 A D F
110307	blood),re-ex	Cells	Cora Biooa			ZAP Express
H0590	Human adult small	Human Adult	Small Int.			II : ZAD VD
110370	intestine,re-excision	Small Intestine	Siliali IIII.			Uni-ZAP XR
H0591	Human T-cell	T-Cell	T C-11	<u> </u>	4:	TILL TARKS
110371	lymphoma;re-excision	Lymphoma	T-Cell		disease	Uni-ZAP XR
110502						
H0592	Healing groin wound - zero hr post-incision	HGS wound	,		disease	pCMVSport 3.0
		healing project;				
H0593	(control)	abdomen				
H0593	Olfactory	Olfactory				pCMVSport 3.0
ļ	epithelium;nasalcavity	epithelium from	,	i		
İ		roof of left nasal				
TIOCOL	11	cacit				
H0594	Human Lung Cancer;re-	Human Lung	Lung		disease	Lambda ZAP II
TIOSOS	excision	Cancer				
H0595	Stomach cancer	Stomach Cancer			disease	Uni-ZAP XR
	(human);re-excision	- 5383A (human)				
110505		Uluman Calan	Colon			Lambda ZAP II
H0596	Human Colon Cancer;re-	Human Colon				
	excision	Cancer				
H0597	excision Human Colon; re-excision	Cancer Human Colon				Lambda ZAP II
	excision	Cancer	Stomach			Lambda ZAP II Uni-ZAP XR

H0599	Human Adult Heart;re- excision	Human Adult Heart	Heart		Uni-ZAP XR
H0600	Healing Abdomen wound;70&90 min post incision	Abdomen		disease	pCMVSport 3.0
H0601	Healing Abdomen Wound;15 days post incision	Abdomen		disease	pCMVSport 3.0
H0602	Healing Abdomen Wound;21&29 days post incision	Abdomen	·	disease	pCMVSport 3.0
H0604	Human Pituitary, re- excision	Human Pituitary			pBluescript
H0606	Human Primary Breast Cancer;re-excision	Human Primary Breast Cancer	Breast	disease	Uni-ZAP XR
H0607	H.Leukocytes, normalized cot 50A3	H.Leukocytes			pCMVSport 1
H0610	H. Leukocytes, normalized cot 5A	H.Leukocytes			pCMVSport 1
H0611	H. Leukocytes, normalized cot 500 B	H.Leukocytes			pCMVSport 1
H0612	H.Leukocytes, normalized cot 50 B	H.Leukocytes			pCMVSport 1
H0613	H.Leukocytes, normalized cot 5B	H.Leukocytes			pCMVSport 1
H0615	Human Ovarian Cancer Reexcision	Ovarian Cancer	Ovary	disease	Uni-ZAP XR
H0616	Human Testes, Reexcision	Human Testes	Testis		Uni-ZAP XR
H0617	Human Primary Breast Cancer Reexcision	Human Primary Breast Cancer	Breast	disease	Uni-ZAP XR
H0618	Human Adult Testes, Large Inserts, Reexcision	Human Adult Testis	Testis		Uni-ZAP XR
H0619	Fetal Heart	Human Fetal Heart	Heart		Uni-ZAP XR
H0620	Human Fetal Kidney; Reexcision	Human Fetal Kidney	Kidney		Uni-ZAP XR
H0622	Human Pancreas Tumor; Reexcision	Human Pancreas Tumor	Pancreas	disease	Uni-ZAP XR
H0623	Human Umbilical Vein; Reexcision	Human Umbilical Vein Endothelial Cells	Umbilical vein		Uni-ZAP XR
H0624	12 Week Early Stage Human II; Reexcision	Twelve Week Old Early Stage Human	Embryo		Uni-ZAP XR
H0625	Ku 812F Basophils Line	Ku 812F Basophils			pSport1
H0626	Saos2 Cells; Untreated	Saos2 Cell Line; Untreated			pSport1
H0627	Saos2 Cells; Vitamin D3 Treated	Saos2 Cell Line; Vitamin D3 Treated			pSport1
H0628	Human Pre-Differentiated Adipocytes	Human Pre- Differentiated Adipocytes			Uni-ZAP XR
H0629	Human Leukocyte, control #2	Human Normalized leukocyte			pCMVSport 1
H0630	Human Leukocytes,normalized control #4	Human Normalized leukocyte			pCMVSport 1
H0631	Saos2, Dexamethosome Treated	Saos2 Cell Line; Dexamethosome Treated			pSport1
H0632	Hepatocellular Tumor;re- excision	Hepatocellular Tumor	Liver		Lambda ZAP II

110622	11 0					
H0633	Lung Carcinoma A549 TNFalpha activated	TNFalpha activated A549			disease	pSport1
	11vi aipiia activated	Lung Carcinoma				
H0634	Human Testes Tumor, re-	Human Testes	Testis	 	disease	Uni-ZAP XR
	excision	Tumor	1		uiscase	Oll-ZAI AK
H0635	Human Activated T-Cells,	Activated T-	Blood	Cell Line		Uni-ZAP XR
	re-excision	Cells				
H0637	Dendritic Cells From	Dentritic cells				pSport1
110/20	CD34 Cells	from CD34 cells	<u> </u>			
H0638	CD40 activated monocyte dendridic cells	CD40 activated				pSport1
	delidifate cens	monocyte dendridic cells				
H0640	Ficolled Human Stromal	Ficolled Human	· · · · · · · · · · · · · · · · · · ·	+		Other
	Cells, Untreated	Stromal Cells,				Oulei
		Untreated				
H0641	LPS activated derived	LPS activated				pSport1
	dendritic cells	monocyte				1
		derived dendritic	į.	,		
H0642	Hep G2 Cells, lambda	cells		 	ļ	
П0042	library	Hep G2 Cells		1		Other
H0643	Hep G2 Cells, PCR library	Hep G2 Cells	<u> </u>	-		Other
H0644	Human Placenta (re-	Human Placenta	Placenta		 	Other Uni-ZAP XR
	excision)	Incoma	1 iuccina	1		OIII-ZAF AK
H0645	Fetal Heart, re-excision	Human Fetal	Heart	1		Uni-ZAP XR
		Heart				
H0646	Lung, Cancer (4005313	Metastatic				pSport1
	A3): Invasive Poorly Differentiated Lung	squamous cell				
	Adenocarcinoma,	lung carcinoma, poorly di		1		
H0647	Lung, Cancer (4005163	Invasive poorly			disease	pSport1
	B7): Invasive, Poorly Diff.	differentiated			uisease	рэрон
	Adenocarcinoma,	lung				
	Metastatic	adenocarcinoma				
H0648	Ovary, Cancer: (4004562	Papillary Cstic			disease	pSport1
	B6) Papillary Serous Cystic Neoplasm, Low	neoplasm of low				
	Malignant Pot	malignant potentia				
H0649	Lung, Normal: (4005313	Normal Lung				pSport1
	B1)	1 torniar Dung				popolti
H0650	B-Cells	B-Cells				pCMVSport 3.0
H0651	Ovary, Normal:	Normal Ovary				pSport1
	(9805C040R)					
H0652	Lung, Normal: (4005313	Normal Lung				pSport1
H0653	B1) Stromal Cells	Stromal Calla				
H0654	Lung, Cancer: (4005313	Stromal Cells Metastatic				pSport1 Other
11000	A3) Invasive Poorly-	Squamous cell				Other
	differentiated Metastatic	lung Carcinoma				
	lung adenoc	poorly dif		<u> </u>		
H0656	B-cells (unstimulated)	B-cells				pSport1
H0657	D calle (attended 2)	(unstimulated)				
H0657	B-cells (stimulated)	B-cells]		pSport1
H0658	Ovary, Cancer	(stimulated) 9809C332-	Ovary &		dingsss	-C1
110030	(9809C332): Poorly	9809C332- Poorly	Fallopian		disease	pSport1
	differentiated	differentiate	Tubes			
	adenocarcinoma			[
H0659	Ovary, Cancer	Grade II	Ovary		disease	pSport1
	(15395A1F): Grade II	Papillary				=
	Papillary Carcinoma	Carcinoma,				
	. ,			. 1		
H0660		Ovary		 	1:	- C
H0660	Ovary, Cancer:	Poorly			disease	pSport1
H0660					disease	pSport1

	A5)				
H0662	Breast, Normal: (4005522B2)	Normal Breast - #4005522(B2)	Breast		pSport1
H0663	Breast, Cancer: (4005522 A2)	Breast Cancer - #4005522(A2)	Breast	disease	pSport1
H0664	Breast, Cancer: (9806C012R)	Breast Cancer	Breast	disease	pSport1
H0665	Stromal cells 3.88	Stromal cells 3.88			pSport1
H0666	Ovary, Cancer: (4004332 A2)	Ovarian Cancer, Sample #4004332A2		disease	pSport1
H0667	Stromal cells(HBM3.18)	Stromal cell(HBM 3.18)			pSport1
H0668	stromal cell clone 2.5	stromal cell clone 2.5			pSport1
H0669	Breast, Cancer: (4005385 A2)	Breast Cancer (4005385A2)	Breast		pSport1
Н0670	Ovary, Cancer(4004650 A3): Well-Differentiated Micropapillary Serous Carcinoma	Ovarian Cancer - 4004650A3			pSport1
H0671	Breast, Cancer: (9802C02OE)	Breast Cancer- Sample # 9802C02OE			pSport1
H0672	Ovary, Cancer: (4004576 A8)	Ovarian Cancer(4004576 A8)	Ovary		pSport1
H0673	Human Prostate Cancer, Stage B2; re-excision	Human Prostate Cancer, stage B2	Prostate		Uni-ZAP XR
H0674	Human Prostate Cancer, Stage C; re-excission	Human Prostate Cancer, stage C	Prostate		Uni-ZAP XR
H0675	Colon, Cancer: (9808C064R)	Colon Cancer 9808C064R			pCMVSport 3.0
H0676	Colon, Cancer: (9808C064R)-total RNA	Colon Cancer 9808C064R			pCMVSport 3.0
H0677	TNFR degenerate oligo	B-Cells			PCRII
H0682	Serous Papillary Adenocarcinoma	serous papillary adenocarcinoma (9606G304SPA3 B)			pCMVSport 3.0
H0683	Ovarian Serous Papillary Adenocarcinoma	Serous papillary adenocarcinoma, stage 3C (9804G01			pCMVSport 3.0
H0684	Serous Papillary Adenocarcinoma	Ovarian Cancer- 9810G606	Ovaries		pCMVSport 3.0
H0685	Adenocarcinoma of Ovary, Human Cell Line, # OVCAR-3	Adenocarcinoma of Ovary, Human Cell Line, # OVCAR-			pCMVSport 3.0
H0686	Adenocarcinoma of Ovary, Human Cell Line	Adenocarcinoma of Ovary, Human Cell Line, # SW- 626			pCMVSport 3.0
Н0687	Human normal ovary(#9610G215)	Human normal ovary(#9610G21 5)	Ovary		pCMVSport 3.0
H0688	Human Ovarian Cancer(#9807G017)	Human Ovarian cancer(#9807G0 17),mRNA from Maura Ru			pCMVSport 3.0
H0689	Ovarian Cancer	Ovarian Cancer, #9806G019			pCMVSport 3.0
H0690	Ovarian Cancer, # 9702G001	Ovarian Cancer, #9702G001			pCMVSport 3.0

H0691	Normal Ovary, #9710G208	normal ovary, #9710G208				pCMVSport 3.0
H0692	BLyS Receptor from Expression Cloning	B Cell Lymphoma	B Cell			pCMVSport 3.0
H0693	Normal Prostate #ODQ3958EN	Normal Prostate Tissue # ODQ3958EN			_	pCMVSport 3.0
H0694	Prostate gland adenocarcinoma	Prostate gland, adenocarcinoma, mod/diff, gleason	prostate gland			pCMVSport 3.0
H0695	mononucleocytes from patient	mononucleocytes from patient at Shady Grove Hospit				pCMVSport 3.0
N0006	Human Fetal Brain	Human Fetal Brain				
N0007	Human Hippocampus	Human Hippocampus				
S0001	Brain frontal cortex	Brain frontal cortex	Brain			Lambda ZAP II
S0002	Monocyte activated	Monocyte- activated	blood .	Cell Line		Uni-ZAP XR
S0003	Human Osteoclastoma	Osteoclastoma	bone		disease	Uni-ZAP XR
S0004	Prostate	Prostate BPH	Prostate			Lambda ZAP II
S0005	Heart	Heart-left ventricle	Heart			pCDNA
S0006	Neuroblastoma	Human Neural Blastoma			disease	pCDNA
S0007	Early Stage Human Brain	Human Fetal Brain				Uni-ZAP XR
S0010	Human Amygdala	Amygdala				Uni-ZAP XR
S0011	STROMAL - OSTEOCLASTOMA	Osteoclastoma	bone		disease	Uni-ZAP XR
S0013	Prostate	Prostate	prostate			Uni-ZAP XR
S0014	Kidney Cortex	Kidney cortex	Kidney			Uni-ZAP XR
S0015	Kidney medulla	Kidney medulla	Kidney			Uni-ZAP XR
S0016	Kidney Pyramids	Kidney pyramids	Kidney			Uni-ZAP XR
S0022	Human Osteoclastoma Stromal Cells - unamplified	Osteoclastoma Stromal Cells				Uni-ZAP XR
S0024	Human Kidney Medulla - unamplified	Human Kidney Medulla				
S0026	Stromal cell TF274	stromal cell	Bone marrow	Cell Line		Uni-ZAP XR
S0027	Smooth muscle, serum treated	Smooth muscle	Pulmanary artery	Cell Line		Uni-ZAP XR
S0028	Smooth muscle,control	Smooth muscle	Pulmanary artery	Cell Line		Uni-ZAP XR
S0029	brain stem	Brain stem	brain			Uni-ZAP XR
S0031	Spinal cord	Spinal cord	spinal cord			Uni-ZAP XR
S0032	Smooth muscle-ILb induced	Smooth muscle	Pulmanary artery	Cell Line		Uni-ZAP XR
S0036	Human Substantia Nigra	Human Substantia Nigra				Uni-ZAP XR
S0037	Smooth muscle, IL1b induced	Smooth muscle	Pulmanary artery	Cell Line		Uni-ZAP XR
S0038	Human Whole Brain #2 - Oligo dT > 1.5Kb	Human Whole Brain #2	1			ZAP Express
S0039	Hypothalamus	Hypothalamus	Brain			Uni-ZAP XR
S0040	Adipocytes	Human Adipocytes from Osteoclastoma				Uni-ZAP XR
S0042	Testes	Human Testes				ZAP Express
S0044	Prostate BPH	prostate BPH	Prostate		disease	Uni-ZAP XR
	Endothelial cells-control	Endothelial cell	endothelial	Cell Line		Uni-ZAP XR

			cell-lung			
S0046	Endothelial-induced	Endothelial cell	endothelial cell-lung	Cell Line		Uni-ZAP XR
S0049	Human Brain, Striatum	Human Brain, Striatum				Uni-ZAP XR
S0050	Human Frontal Cortex, Schizophrenia	Human Frontal Cortex, Schizophrenia			disease	Uni-ZAP XR
S0051	Human Hypothalmus,Schizophren ia	Human Hypothalamus, Schizophrenia			disease	Uni-ZAP XR
S0052	neutrophils control	human neutrophils	blood	Cell Line		Uni-ZAP XR
S0053	Neutrophils IL-1 and LPS induced	human neutrophil induced	blood	Cell Line		Uni-ZAP XR
S0106	STRIATUM DEPRESSION		BRAIN		disease	Uni-ZAP XR
S0110	Brain Amygdala Depression		Brain		disease	Uni-ZAP XR
S0112	Hypothalamus		Brain			Uni-ZAP XR
S0114	Anergic T-cell	Anergic T-cell		Cell Line		Uni-ZAP XR
S0114 S0116	Bone marrow	Bone marrow	Bone marrow	CON LINE		Uni-ZAP XR
S0118	Smooth muscle control 2	Smooth muscle	Pulmanary artery	Cell Line		Uni-ZAP XR
S0122	Osteoclastoma-normalized A	Osteoclastoma	bone		disease	pBluescript
S0124	Smooth muscle-edited A	Smooth muscle	Pulmanary artery	Cell Line		Uni-ZAP XR
S0126	Osteoblasts	Osteoblasts	Knee	Cell Line		Uni-ZAP XR
S0132	Epithelial-TNFa and INF induced	Airway Epithelial				Uni-ZAP XR
S0134	Apoptotic T-cell	apoptotic cells		Cell Line		Uni-ZAP XR
S0136	PERM TF274	stromal cell	Bone marrow	Cell Line		Lambda ZAP II
S0140	eosinophil-IL5 induced	eosinophil	lung	Cell Line		Uni-ZAP XR
S0142	Macrophage-oxLDL	macrophage- oxidized LDL treated	blood	Cell Line		Uni-ZAP XR
S0144	Macrophage (GM-CSF treated)	Macrophage (GM-CSF treated)				Uni-ZAP XR
S0146	prostate-edited		Prostata			IIm: ZAD VD
S0146 S0148		prostate BPH	Prostate			Uni-ZAP XR
S0148 S0150	Normal Prostate LNCAP prostate cell line	Prostate LNCAP Cell	prostate	Call I ima		Uni-ZAP XR
S0150 S0152	PC3 Prostate cell line	Line PC3 prostate cell	Prostate	Cell Line		Uni-ZAP XR
S0152 S0174	Prostate-BPH subtracted II	line Human Prostate				Uni-ZAP XR pBluescript
S0174		BPH	mpostat-			
	Prostate, normal, subtraction I	Prostate	prostate		1.	Uni-ZAP XR
S0180	Bone Marrow Stroma, TNF&LPS ind	Bone Marrow Stroma, TNF & LPS induced			disease	Uni-ZAP XR
S0182	Human B Cell 8866	Human B- Cell 8866				Uni-ZAP XR
S0188	Prostate,BPH, Lib 2	Human Prostate BPH			disease	pSport1
S0190	Prostate BPH,Lib 2, subtracted	Human Prostate BPH				pSport1
S0192	Synovial Fibroblasts (control)	Synovial Fibroblasts				pSport1
S0194	Synovial hypoxia	Synovial Fibroblasts				pSport1

S0196	Synovial IL-1/TNF	Synovial				pSport1
50207	stimulated Smooth Muscle- HASTE	Fibroblasts	D 1	C III		
S0206	normalized	Smooth muscle	Pulmanary artery	Cell Line		pBluescript
S0208	Messangial cell, frac 1	Messangial cell				pSport1
S0210	Messangial cell, frac 2	Messangial cell				pSport1
S0212	Bone Marrow Stromal Cell, untreated	Bone Marrow Stromal Cell,untreated				pSport1
S0214	Human Osteoclastoma, re- excision	Osteoclastoma	bone		disease	Uni-ZAP XR
S0216	Neutrophils IL-1 and LPS induced	human neutrophil induced	blood	Cell Line		Uni-ZAP XR
S0218	Apoptotic T-cell, re- excision	apoptotic cells		Cell Line		Uni-ZAP XR
S0220	H. hypothalamus, frac A;re-excision	Hypothalamus	Brain			ZAP Express
S0222	H. Frontal cortex,epileptic;re- excision	H. Brain, Frontal Cortex, Epileptic	Brain		disease	Uni-ZAP XR
S0242	Synovial Fibroblasts (II1/TNF), subt	Synovial Fibroblasts				pSport1
S0250	Human Osteoblasts II	Human Osteoblasts	Femur		disease	pCMVSport 2.0
S0260	Spinal Cord, re-excision	Spinal cord	spinal cord			Uni-ZAP XR
S0270	PTMIX	PTMIX (Human Thymus)	Thymus			PCRII
S0276	Synovial hypoxia-RSF subtracted	Synovial fobroblasts (rheumatoid)	Synovial tissue			pSport1
S0278	H Macrophage (GM-CSF treated), re-excision	Macrophage (GM-CSF treated)				Uni-ZAP XR
S0280	Human Adipose Tissue, re-excision	Human Adipose Tissue				Uni-ZAP XR
S0282	Brain Frontal Cortex, re- excision	Brain frontal cortex	Brain			Lambda ZAP II
S0292	Osteoarthritis (OA-4)	Human Osteoarthritic Cartilage	Bone		disease	pSport1
S0294	Larynx tumor	Larynx tumor	Larynx,voc al cord		disease	pSport1
S0296	Normal lung	Normal lung	Lung			pSport1
S0298	Bone marrow	Bone marrow	Bone			pSport1
S0300	stroma, treated Frontal lobe, dementia; re-	stroma,treatedSB Frontal Lobe	marrow Brain			Uni-ZAP XR
50206	excision	dementia/Alzhei mer"s				G
S0306	Larynx normal #10 261- 273	Larynx normal				pSport1
S0308 S0310	Spleen/normal Normal trachea	Spleen normal Normal trachea				pSport1
S0310 S0312	Human	Normai tracnea Human			disease	pSport1
50312	osteoarthritic;fraction II	osteoarthritic cartilage			uisease	pSport1
S0314	Human osteoarthritis;fraction I	Human osteoarthritic cartilage			disease	pSport1
S0316	Human Normal Cartilage,Fraction I	Human Normal Cartilage				pSport1
S0318	Human Normal Cartilage Fraction II	Human Normal Cartilage				pSport1
S0322	Siebben Polyposis	Siebben Polyposis				pSport1
S0328	Palate carcinoma	Palate carcinoma	Uvula		disease	pSport1

S0330	Palate normal	Palate normal	Uvula			pSport1
S0332	Pharynx carcinoma	Pharynx	Hypopharyn	<u> </u>		pSport1
		carcinoma	х			
S0334	Human Normal Cartilage Fraction III	Human Normal Cartilage			1	pSport1
S0338	Human Osteoarthritic	Human			disease	pSport1
	Cartilage Fraction III	osteoarthritic				
S0342	Adipocytes;re-excision	cartilage Human			<u> </u>	Uni-ZAP XR
505-2	Adipocytes, re-excision	Adipocytes from			j	UIII-ZAP AR
		Osteoclastoma				
S0344	Macrophage-oxLDL; re-	macrophage-	blood	Cell Line		Uni-ZAP XR
	excision	oxidized LDL				
S0346	Human Amundalama	treated				11111111111
30346	Human Amygdala;re- excision	Amygdala				Uni-ZAP XR
S0348	Cheek Carcinoma	Cheek			disease	pSport1
		Carcinoma			Libease	poporti
S0350	Pharynx Carcinoma	Pharynx	Hypopharyn		disease	pSport1
200.50		carcinoma	х			
S0352	Larynx Carcinoma	Larynx carcinoma			disease	pSport1
S0354	Colon Normal II	Colon Normal	Colon			pSport1
S0356	Colon Carcinoma	Colon Carcinoma	Colon		disease	pSport1
S0358	Colon Normal III	Colon Normal	Colon		discase	pSport1
S0360	Colon Tumor II	Colon Tumor	Colon		disease	pSport1
S0362	Human Gastrocnemius	Gastrocnemius				pSport1
		muscle				
S0364	Human Quadriceps	Quadriceps				pSport1
S0366	Human Soleus	muscle				0 11
S0370	Larynx carcinoma II	Soleus Muscle Larynx			diasas	pSport1
30370	Larynx caremonia n	carcinoma			disease	pSport1
S0372	Larynx carcinoma III	Larynx			disease	pSport1
		carcinoma				popo
S0374	Normal colon	Normal colon				pSport1
S0376	Colon Tumor	Colon Tumor			disease	pSport1
S0378	Pancreas normal PCA4	Pancreas Normal				pSport1
S0380	No Pancreas Tumor PCA4 Tu	PCA4 No Pancreas Tumor			1:	-0
30360	rancicas funioi FCA4 fu	PCA4 Tu			disease	pSport1
S0382	Larynx carcinoma IV	Larynx			disease	pSport1
		carcinoma				
S0384	Tongue carcinoma	Tongue			disease	pSport1
00206	II 3371 1 75 :	carcinoma				
S0386	Human Whole Brain, re- excision	, Whole brain	Brain			ZAP Express
S0388	Human	Human			disease	Uni-ZAP XR
	Hypothalamus, schizophre	Hypothalamus,			uiscasc	OIII-ZAI AK
	nia, re-excision	Schizophrenia				
S0390	Smooth muscle, control;	Smooth muscle	Pulmanary	Cell Line		Uni-ZAP XR
S0392	re-excision	6.1:	artery			
30392	Salivary Gland	Salivary gland; normal				pSport1
S0394	Stomach;normal	Stomach; normal				pSport1
50398	Testis; normal	Testis; normal				pSport1
50400	Brain; normal	Brain; normal				pSport1
S0402	Adrenal Gland, normal	Adrenal gland;				pSport1
		normal				
50404	Rectum normal	Rectum, normal				pSport1
50406	Rectum tumour	Rectum tumour				pSport1
50408	Colon, normal	Colon, normal				pSport1
	Colon turner					
S0410 S0412	Colon, tumour Temporal cortex-	Colon, tumour Temporal cortex,			disease	pSport1 Other

		T		,		Lou
S0414	Hippocampus, Alzheimer	Hippocampus,				Other
	Subtracted	Alzheimer				
		Subtracted				GI (IVG
S0418	CHME Cell Line;treated 5	CHME Cell				pCMVSport 3.0
20.100	hrs	Line; treated				
S0420	CHME Cell	CHME Cell line,		:		pSport1
	Line,untreated	untreatetd				
S0422	Mo7e Cell Line GM-CSF	Mo7e Cell Line		!		pCMVSport 3.0
	treated (1ng/ml)	GM-CSF treated				
		(lng/ml)				
S0424	TF-1 Cell Line GM-CSF	TF-1 Cell Line				pSport1
00406	Treated	GM-CSF Treated		G 11 T :		11 57 5 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7
S0426	Monocyte activated; re-	Monocyte-	blood	Cell Line		Uni-ZAP XR
50400	excision	activated	11 1	C II I		II : ZADVD
S0428	Neutrophils control; re-	human	blood	Cell Line		Uni-ZAP XR
00400	excision	neutrophils				0 11
S0430	Aryepiglottis Normal	Aryepiglottis				pSport1
00422	G:	Normal				C
S0432	Sinus piniformis Tumour	Sinus piniformis				pSport1
50424	Ctamach Nammal	Tumour			diagona	mCmowt1
S0434	Stomach Normal Stomach Tumour	Stomach Normal			disease	pSport1
S0436	Liver Normal Met5No	Stomach Tumour			disease	pSport1
S0438	Liver Normal Met5No	Liver Normal				pSport1
50440	Lines Trees and M. C. T.	Met5No		ļ		
S0440	Liver Tumour Met 5 Tu	Liver Tumour		ļ		pSport1
S0442	Colon Normal	Colon Normal			.	pSport1
S0444	Colon Tumor	Colon Tumour			disease	pSport1
S0446	Tongue Tumour	Tongue Tumour				pSport1
S0448	Larynx Normal	Larynx Normal				pSport1
S0450	Larynx Tumour	Larynx Tumour				pSport1
S0452	Thymus	Thymus				pSport1
S0454	Placenta	Placenta	Placenta			pSport1
S0456	Tongue Normal	Tongue Normal				pSport1
S0458	Thyroid Normal (SDCA2 No)	Thyroid normal				pSport1
S0460	Thyroid Tumour	Thyroid Tumour				pSport1
S0462	Thyroid Thyroiditis	Thyroid				pSport1
	•	Thyroiditis		}		1
S0464	Larynx Normal	Larynx Normal				pSport1
S0468	Ea.hy.926 cell line	Ea.hy.926 cell				pSport1
	,	line				1
S0470	Adenocarcinoma	PYFD			disease	pSport1
S0472	Lung Mesothelium	PYBT		1		pSport1
S0474	Human blood platelets	Platelets	Blood			Other
	<u> </u>		platelets			
S0665	Human Amygdala; re- excission	Amygdala				Uni-ZAP XR
S3012	Smooth Muscle Serum Treated, Norm	Smooth muscle	Pulmanary artery	Cell Line		pBluescript
S3014	Smooth muscle, serum induced,re-exc	Smooth muscle	Pulmanary artery	Cell Line		pBluescript
S6014	H. hypothalamus, frac A	Hypothalamus	Brain	1		ZAP Express
S6016	H. Frontal Cortex,	H. Brain, Frontal	Brain		disease	Uni-ZAP XR
	Epileptic	Cortex, Epileptic				
S6022	H. Adipose Tissue	Human Adipose Tissue				Uni-ZAP XR
S6024	Alzheimers, spongy change	Alzheimer"s/Spo ngy change	Brain		disease	Uni-ZAP XR
S6026	Frontal Lobe, Dementia	Frontal Lobe dementia/Alzhei	Brain			Uni-ZAP XR
1		mer"s				
			D		disease	Uni-ZAP XR
S6028	Human Manic Depression Tissue	Human Manic depression tissue	Brain		uisease	

T0002	Activated T-cells	Activated T-Cell,	Blood	Cell Line		pBluescript SK-
T0003	Human Fetal Lung	PBL fraction Human Fetal				pBluescript SK-
T0004		Lung				
T0004	Human White Fat	Human White Fat				pBluescript SK-
T0006	Human Pineal Gland	Human Pinneal Gland	!			pBluescript SK-
T0008	Colorectal Tumor	Colorectal Tumor			disease	pBluescript SK-
T0010	Human Infant Brain	Human Infant Brain				Other
T0023	Human Pancreatic	Human			disease	pBluescript SK-
	Carcinoma	Pancreatic				
T0039	HSA 172 Cells	Carcinoma Human HSA 172		+		pBluescript SK-
10005	172 CONS	cell line				pBlacscript Six-
T0040	HSC172 cells	SA172 Cells				pBluescript SK-
T0041	Jurkat T-cell G1 phase	Jurkat T-cell				pBluescript SK-
T0042	Jurkat T-Cell, S phase	Jurkat T-Cell Line				pBluescript SK-
T0048	Human Aortic Endothelium	Human Aortic Endothilium				pBluescript SK-
T0049	Aorta endothelial cells + TNF-a	Aorta endothelial cells				pBluescript SK-
T0060	Human White Adipose	Human White Fat				pBluescript SK-
T0067	Human Thyroid	Human Thyroid				pBluescript SK-
T0068	Normal Ovary, Premenopausal	Normal Ovary, Premenopausal				pBluescript SK-
T0069	Human Uterus, normal	Human Uterus, normal				pBluescript SK-
T0071	Human Bone Marrow	Human Bone Marrow				pBluescript SK-
T0078	Human Liver, normal adult	Human Liver, normal Adult				pBluescript SK-
T0082	Human Adult Retina	Human Adult Retina		,		pBluescript SK-
T0090	Liver, normal		•			pBluescript SK-
T0104	HCC cell line metastisis to liver					pBluescript SK-
T0109	Human (HCC) cell line liver (mouse) metastasis, remake					pBluescript SK-
T0110	Human colon carcinoma (HCC) cell line, remake					pBluescript SK-
T0112	Human (Caco-2) cell line, adenocarcinoma, colon					pBluescript SK-
T0114	Human (Caco-2) cell line, adenocarcinoma, colon, remake					pBluescript SK-
T0115	Human Colon Carcinoma (HCC) cell line					pBluescript SK-
L0002	Atrium cDNA library Human heart					
L0004	ClonTech HL 1065a			1		
L0005	Clontech human aorta polyA+ mRNA (#6572)					
L0009	EST from 8p21.3-p22			 		
L0015	Human					
L0021	Human adult (K.Okubo)					
L0022	Human adult lung 3" directed Mbol cDNA					
L0032	Human chromosome 12p cDNAs					

						···
L0040	Human colon mucosa				<u> </u>	
L0041	Human epidermal					
	keratinocyte					
L0045	Human keratinocyte					
	differential display		ł			
İ	(B.Lin)					
L0052	Human normalized K562-					
	cDNA					
L0055	Human promyelocyte					
L0060	Human thymus NSTH II					
L0065	Liver HepG2 cell line.					
L0103	DKFZphamy1	amygdala				
L0105	Human aorta polyA+	aorta				
L0103	(TFujiwara)	aorta				
L0109	Human brain cDNA	brain				
L0109 L0118	Human fetal brain S.	brain				
TO119		Utalli				
T 0100	Meier-Ewert	named singing				
L0138	Human normal gingiva	normal gingiva			<u> </u>	
L0142	Human placenta cDNA	placenta				1
	(TFujiwara)					
L0143	Human placenta polyA+	placenta				
	(TFujiwara)				 	ļ
L0149	DKFZphsnu1	subthalamic				
		nucleus			<u> </u>	ļ
L0151	Human testis (C. De	testis			!	
	Smet)					
L0157	Human fetal brain		brain			
	(TFujiwara)					
L0163	Human heart cDNA		heart		1	ł
	(YNakamura)					
L0194	Human pancreatic cancer	pancreatic cancer		Patu		
	cell line Patu 8988t			8988t		
L0351	Infant brain, Bento Soares					BA, M13-derived
L0352	Normalized infant brain,					BA, M13-derived
1	Bento Soares					
L0361	Stratagene ovary		ovary			Bluescript SK
	(#937217)					
L0362	Stratagene ovarian cancer				1	Bluescript SK-
	(#937219)					
L0363	NCI_CGAP_GC2	germ cell tumor				Bluescript SK-
L0364	NCI_CGAP_GC5	germ cell tumor				Bluescript SK-
L0365	NCI_CGAP_Phe1	pheochromocyto				Bluescript SK-
20000		ma			1	
L0366	Stratagene schizo brain	schizophrenic				Bluescript SK-
1 20500	S11	brain S-11				
		frontal lobe				
L0367	NCI_CGAP_Sch1	Schwannoma				Bluescript SK-
~~~		tumor				<u> </u>
L0368	NCI_CGAP_SS1	synovial sarcoma				Bluescript SK-
L0369	NCI_CGAP_AA1	adrenal adenoma	adrenal			Bluescript SK-
1 50309	INCI_COMI_MAI	marchai adoliolila	gland	I	1	
L0370	Johnston frontal cortex	pooled frontal	brain			Bluescript SK-
LU3/U	Johnston Homai Conex	lobe	J	1	1	
L0371	NCI_CGAP_Br3	breast tumor	breast			Bluescript SK-
		colon tumor	colon			Bluescript SK-
L0372	NCI_CGAP_Co12		colon	ļ	+	Bluescript SK-
L0373	NCI_CGAP_Co11	tumor			<del> </del>	Bluescript SK-
L0374	NCI_CGAP_Co2	tumor	colon	<del> </del>	<del> </del>	
L0375	NCI_CGAP_Kid6	kidney tumor	kidney		<b>_</b>	Bluescript SK-
L0376	NCI_CGAP_Lar1	larynx	larynx			Bluescript SK-
L0377	NCI_CGAP_HN2	squamous cell	larynx			Bluescript SK-
		carcinoma from	1	ļ	1	
		vocal cord	<del> </del>		.	Dia : CY
L0378	NCI_CGAP_Lu1	lung tumor	lung	ļ	<b></b>	Bluescript SK-
L0379	NCI_CGAP_Lym3	lymphoma	lymph node	<u> </u>	_1	Bluescript SK-

		<del></del>	1	г	
L0380	NCI_CGAP_HN1	squamous cell carcinoma	lymph node		Bluescript SK-
L0381	NCI_CGAP_HN4	squamous cell carcinoma	pharynx		Bluescript SK-
L0382	NCI_CGAP_Pr25	epithelium (cell line)	prostate		Bluescript SK-
L0383	NCI_CGAP_Pr24	invasive tumor (cell line)	prostate		Bluescript SK-
L0384	NCI_CGAP_Pr23	prostate tumor	prostate		Bluescript SK-
L0386	NCI_CGAP_HN3	squamous cell	tongue		Bluescript SK-
20000		carcinoma from base of tongue	l		2.000
L0387	NCI_CGAP_GCB0	germinal center B-cells	tonsil		Bluescript SK-
L0388	NCI_CGAP_HN6	normal gingiva (cell line from immortalized kerati			Bluescript SK-
L0389	NCI_CGAP_HN5	normal gingiva (cell line from primary keratinocyt			Bluescript SK-
L0393	B, Human Liver tissue				gt11
L0394	H, Human adult Brain Cortex tissue				gt11
L0411	1-NIB				Lafmid BA
L0415	b4HB3MA Cot8-HAP-Ft				Lafmid BA
L0422	b4HB3MA-Cot12-HAP-B				Lafmid BA
L0426	b4HB3MA-Cot51.5-HAP- Ft				Lafmid BA
L0435	Infant brain, LLNL array of Dr. M. Soares 1NIB				lafmid BA
L0438	normalized infant brain cDNA	total brain	brain		lafmid BA
L0439	Soares infant brain 1NIB		whole brain		Lafmid BA
L0443	ь4НВ3МК				Lafmid BK
L0447	NHB3MK				Lafmid BK
L0448	3HFLSK20				Lafmid K
L0451	N3HFLSK20				Lafmid K
L0453	BATM1				lambda gt10
L0455	Human retina cDNA randomly primed sublibrary	retina	eye		lambda gt10
L0456	Human retina cDNA Tsp5091-cleaved sublibrary	retina	eye		lambda gt10
L0457	multi-tissue normalized short-fragment	multi-tissue	pooled		lambda gt10
L0459	Adult heart, Clontech				Lambda gt11
L0462	WATM1				lambda gt11
L0468	HE6W				lambda zap
L0469	T, Human adult Rhabdomyosarcoma cell- line				Lambda Zap
L0470	BL29 Burkitt"s lymphoma, Pascalis Sideras				lambda ZAP 2
L0471	Human fetal heart, Lambda ZAP Express				Lambda ZAP Express
L0475	KG1-a Lambda Zap Express cDNA library			KG1-a	Lambda Zap Express (Stratagene)
L0477	HPLA CCLee	placenta			Lambda ZAP II
L0480	Stratagene cat#937212				Lambda ZAP,
	(1992)				pBluescript SK(-

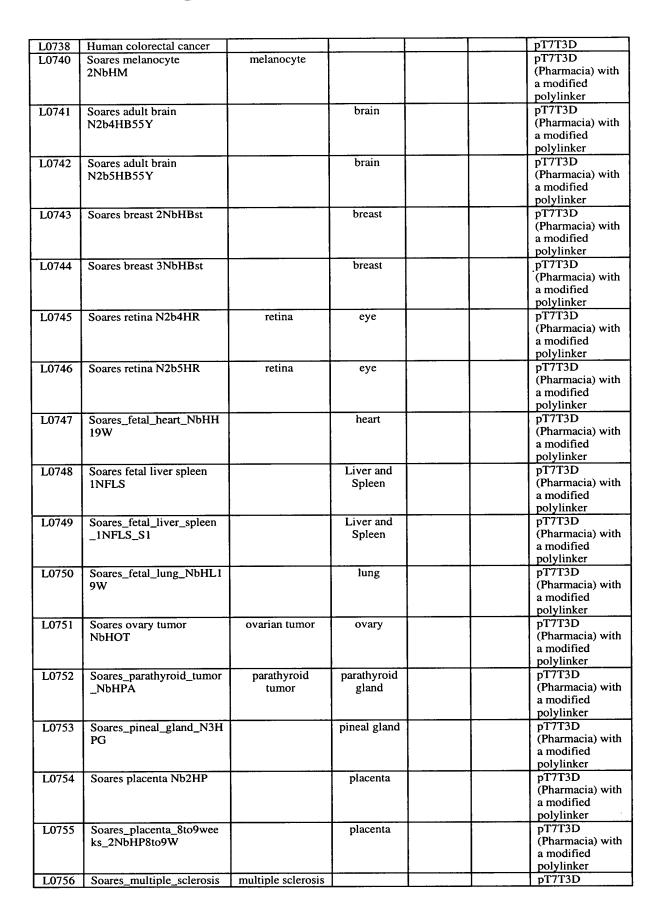
	I	i .		
L0481	CD34+DIRECTIONAL			Lambda ZAPII
L0483	Human pancreatic islet			Lambda ZAPII
L0485	STRATAGENE Human skeletal muscle cDNA library, cat. #936215.	skeletal muscle	leg muscle	Lambda ZAPII
L0493	NCI_CGAP_Ov26	papillary serous carcinoma	ovary	pAMP1
L0497	NCI_CGAP_HSC4	CD34+, CD38- from normal bone marrow donor	bone marrow	pAMP1
L0498	NCI_CGAP_HSC3	CD34+, T negative, patient with chronic myelogenou	bone marrow	pAMP1
L0499	NCI_CGAP_HSC2	stem cell 34+/38+	bone marrow	pAMP1
L0500	NCI_CGAP_Brn20	oligodendroglio ma	brain	pAMP1
L0501	NCI_CGAP_Brn21	oligodendroglio ma	brain	pAMP1
L0502	NCI_CGAP_Br15	adenocarcinoma	breast	pAMP1
L0503	NCI_CGAP_Br17	adenocarcinoma	breast	pAMP1
L0504	NCI_CGAP_Br13	breast carcinoma in situ	breast	pAMP1
L0505	NCI_CGAP_Br12	invasive carcinoma	breast	pAMP1
L0506	NCI_CGAP_Br16	lobullar carcinoma in situ	breast	pAMP1
L0507	NCI_CGAP_Br14	normal epithelium	breast	pAMP1
L0508	NCI_CGAP_Lu25	bronchioalveolar carcinoma	lung	pAMP1
L0509	NCI_CGAP_Lu26	invasive adenocarcinoma	lung	pAMP1
L0510	NCI_CGAP_Ov33	borderline ovarian carcinoma	ovary	pAMP1
L0511	NCI_CGAP_Ov34	borderline ovarian carcinoma	ovary	pAMP1
L0512	NCI_CGAP_Ov36	borderline ovarian carcinoma	ovary	pAMP1
L0513	NCI_CGAP_Ov37	early stage papillary serous carcinoma	ovary	pAMP1
L0514	NCI_CGAP_Ov31	papillary serous carcinoma	ovary	pAMP1
L0515	NCI_CGAP_Ov32	papillary serous carcinoma	ovary	pAMP1
L0516	Chromosome 19p12-p13.1 exon			pAMP10
L0517	NCI_CGAP_Pr1			pAMP10
L0518	NCI_CGAP_Pr2			pAMP10
L0519	NCI_CGAP_Pr3			pAMP10
L0520	NCI_CGAP_Alv1	alveolar rhabdomyosarco ma		pAMP10
L0521	NCI_CGAP_Ew1	Ewing"s sarcoma		pAMP10
L0522	NCI_CGAP_Kid1	kidney		pAMP10
L0523	NCI_CGAP_Lip2	liposarcoma		pAMP10
L0524	NCI_CGAP_Li1	liver		pAMP10
L0525	NCI_CGAP_Li2	liver		pAMP10

	Lyar ag i n''	<del></del>		<del></del>	
L0526	NCI_CGAP_Pr12	metastatic			pAMP10
		prostate bone			
10555	NOT GOLD OF	lesion			
L0527	NCI_CGAP_Ov2	ovary			pAMP10
L0528	NCI_CGAP_Pr5	prostate			pAMP10
L0529	NCI_CGAP_Pr6	prostate			pAMP10
L0530	NCI_CGAP_Pr8	prostate			pAMP10
L0531	NCI_CGAP_Pr20	prostate			pAMP10
		metastasis, liver			<u>l</u> _
L0532	NCI_CGAP_Thy1	thyroid			pAMP10
L0533	NCI_CGAP_HSC1	stem cells	bone		pAMP10
			marrow	<u>                                     </u>	
L0534	Chromosome 7 Fetal	brain	brain		pAMP10
	Brain cDNA Library				<b>'</b>
L0535	NCI_CGAP_Br5	infiltrating ductal	breast		pAMP10
T 0505	NOT COAD D	carcinoma		ļ	
L0536	NCI_CGAP_Br4	normal ductal	breast		pAMP10
7.0500		tissue			
L0539	Chromosome 7 Placental cDNA Library		placenta		pAMP10
L0540	NCI_CGAP_Pr10	invasive prostate	prostate	1	pAMP10
		tumor	prostate		print 10
L0541	NCI_CGAP_Pr7	low-grade	prostate		pAMP10
		prostatic	prostate		Print 10
		neoplasia			
L0542	NCI_CGAP_Pr11	normal prostatic	prostate		pAMP10
		epithelial cells	Problemo		printi 10
L0543	NCI_CGAP_Pr9	normal prostatic	prostate		pAMP10
		epithelial cells	F		P
L0544	NCI_CGAP_Pr4	prostatic	prostate	†	pAMP10
		intraepithelial	F		F
		neoplasia - high			
		grade			
L0545	NCI_CGAP_Pr4.1	prostatic	prostate		pAMP10
		intraepithelial	F	1	F
		neoplasia - high			
		grade			
L0547	NCI_CGAP_Pr16	tumor	prostate	†	pAMP10
L0549	NCI_CGAP_HN10	carcinoma in situ		† †	pAMP10
	_ <b>-</b>	from retromolar			
		trigone		]	
L0550	NCI_CGAP_HN9	normal squamous			pAMP10
		epithelium from			
		retromolar			
	<u> </u>	trigone		]	
L0551	NCI_CGAP_HN7	normal squamous		Ţ	pAMP10
	-	epithelium, floor			1
		of mouth		<u>                                      </u>	
L0554	NCI_CGAP_Li8		liver		pAMP10
L0555	NCI_CGAP_Lu34	large cell	lung		pAMP10
		carcinoma			
L0558	NCI_CGAP_Ov40	endometrioid	ovary		pAMP10
	_	ovarian	•		1.
		metastasis			
L0559	NCI_CGAP_Ov39	papillary serous	ovary		pAMP10
		ovarian			<b> </b>
		metastasis		<u> </u>	<u> </u>
L0561	NCI_CGAP_HN11	normal squamous	tongue		pAMP10
		epithelium		<u> </u>	<u> </u>
L0562	Chromosome 7 HeLa			HeLa cell	pAMP10
	cDNA Library			line;	1
				ATCC	
L0563	Human Bone Marrow	bone marrow			pBluescript
	Stromal Fibroblast				
L0564	Jia bone marrow stroma	bone marrow			pBluescript

		stroma	1	l T	
L0565	Normal Human Trabecular Bone Cells	Bone	Hip		pBluescript
L0581	Stratagene liver (#937224)		liver		pBluescript SK
L0584	Stratagene cDNA library Human heart, cat#936208	·			pBluescript SK(+)
L0586	HTCDL1				pBluescript SK(-
L0587	Stratagene colon HT29 (#937221)				pBluescript SK-
L0588	Stratagene endothelial cell 937223				pBluescript SK-
L0589	Stratagene fetal retina 937202				pBluescript SK-
L0590	Stratagene fibroblast (#937212)				pBluescript SK-
L0591	Stratagene HeLa cell s3 937216				pBluescript SK-
L0592	Stratagene hNT neuron (#937233)				pBluescript SK-
L0593	Stratagene neuroepithelium (#937231)				pBluescript SK-
L0594	Stratagene neuroepithelium NT2RAMI 937234				pBluescript SK-
L0595	Stratagene NT2 neuronal precursor 937230	neuroepithelial cells	brain		pBluescript SK-
L0596	Stratagene colon (#937204)		colon		pBluescript SK-
L0597	Stratagene corneal stroma (#937222)		cornea		pBluescript SK-
L0598	Morton Fetal Cochlea	cochlea	ear		pBluescript SK-
L0599	Stratagene lung (#937210)		lung		pBluescript SK-
L0600	Weizmann Olfactory Epithelium	olfactory epithelium	nose		pBluescript SK-
L0601	Stratagene pancreas (#937208)		pancreas		pBluescript SK-
L0602	Pancreatic Islet	pancreatic islet	pancreas		pBluescript SK-
L0603	Stratagene placenta (#937225)		placenta		pBluescript SK-
L0604	Stratagene muscle 937209	muscle	skeletal muscle		pBluescript SK-
L0605	Stratagene fetal spleen (#937205)	fetal spleen	spleen		pBluescript SK-
L0606	NCI_CGAP_Lym5	follicular lymphoma	lymph node		pBluescript SK-
L0607	NCI_CGAP_Lym6	mantle cell lymphoma	lymph node		pBluescript SK-
L0608	Stratagene lung carcinoma 937218	lung carcinoma	lung	NCI-H69	pBluescript SK-
L0609	Schiller astrocytoma	astrocytoma	brain		pBluescript SK- (Stratagene)
L0611	Schiller meningioma	meningioma	brain		pBluescript SK- (Stratagene)
L0612	Schiller oligodendroglioma	oligodendroglio ma	brain		pBluescript SK- (Stratagene)
L0615	22 week old human fetal liver cDNA library				pBluescriptII SK(-)
L0617	Chromosome 22 exon				pBluescriptIIKS+
L0619	Chromosome 9 exon II				pBluescriptIIKS+
L0622	HM1				pcDNAII (Invitrogen)
L0623	НМ3	pectoral muscle (after			pcDNAII (Invitrogen)

		· · · · · · · · · · · · · · · · · · ·		
	100 CC 1 D 1 D 1	mastectomy)		 pCMV-SPORT2
L0625	NCI_CGAP_AR1	bulk alveolar tumor		
L0626	NCI_CGAP_GC1	bulk germ cell seminoma		pCMV-SPORT2
L0627	NCI_CGAP_Co1	bulk tumor	colon	pCMV-SPORT2
L0628	NCI_CGAP_Ov1	ovary bulk tumor	ovary	pCMV-SPORT2
L0629	NCI_CGAP_Mel3	metastatic melanoma to bowel	bowel (skin primary)	pCMV-SPORT4
L0630	NCI_CGAP_CNS1	substantia nigra	brain	pCMV-SPORT4
L0631	NCI_CGAP_Br7		breast	pCMV-SPORT4
L0632	NCI_CGAP_Li5	hepatic adenoma	liver	pCMV-SPORT4
L0633	NCI_CGAP_Lu6	small cell carcinoma	lung	pCMV-SPORT4
L0634	NCI_CGAP_Ov8	serous adenocarcinoma	ovary	pCMV-SPORT4
L0635	NCI_CGAP_PNS1	dorsal root ganglion	peripheral nervous system	pCMV-SPORT4
L0636	NCI_CGAP_Pit1	four pooled pituitary adenomas	brain	pCMV-SPORT6
L0637	NCI_CGAP_Brn53	three pooled meningiomas	brain	pCMV-SPORT6
L0638	NCI_CGAP_Brn35	tumor, 5 pooled (see description)	brain	pCMV-SPORT6
L0639	NCI_CGAP_Brn52	tumor, 5 pooled (see description)	brain	pCMV-SPORT6
L0640	NCI_CGAP_Br18	four pooled high- grade tumors, including two prima	breast	pCMV-SPORT6
L0641	NCI_CGAP_Co17	juvenile granulosa tumor	colon	pCMV-SPORT6
L0642	NCI_CGAP_Co18	moderately differentiated adenocarcinoma	colon	pCMV-SPORT6
L0643	NCI_CGAP_Co19	moderately differentiated adenocarcinoma	colon	pCMV-SPORT6
L0644	NCI_CGAP_Co20	moderately differentiated adenocarcinoma	colon	pCMV-SPORT6
L0645	NCI_CGAP_Co21	moderately differentiated adenocarcinoma	colon	pCMV-SPORT6
L0646	NCI_CGAP_Co14	moderately- differentiated adenocarcinoma	colon	pCMV-SPORT6
L0647	NCI_CGAP_Sar4	five pooled sarcomas, including myxoid liposarcoma	connective tissue	pCMV-SPORT6
L0648	NCI_CGAP_Eso2	squamous cell carcinoma	esophagus	pCMV-SPORT6
L0649	NCI_CGAP_GU1	2 pooled high- grade transitional cell tumors	genitourinar y tract	pCMV-SPORT6
L0650	NCI_CGAP_Kid13	2 pooled Wilms" tumors, one primary and one metast	kidney	pCMV-SPORT6
L0651	NCI_CGAP_Kid8	renal cell tumor	kidney	pCMV-SPORT6
L0652	NCI_CGAP_Lu27	four pooled	lung	pCMV-SPORT6

		poorly-			
	i i	differentiated			
		adenocarcinomas			STATE OF STATE
L0653	NCI_CGAP_Lu28	two pooled	lung		pCMV-SPORT6
		squamous cell	i	İ	1
		carcinomas			CMV SPORT4
L0654	NCI_CGAP_Lu31.		lung, cell	1	pCMV-SPORT6
			line		"CMV SPORT6
L0655	NCI_CGAP_Lym12	lymphoma,	lymph node		pCMV-SPORT6
1		follicular mixed		1	·
		small and large			
		cell			pCMV-SPORT6
L0656	NCI_CGAP_Ov38	normal	ovary		pew v-broker
		epithelium			pCMV-SPORT6
L0657	NCI_CGAP_Ov23	tumor, 5 pooled	ovary	i i	pelar broker
	20.50.00	(see description)	OVOTI.		pCMV-SPORT6
L0658	NCI_CGAP_Ov35	tumor, 5 pooled	ovary		peint broker
	100 00 D D	(see description) adenocarcinoma	manarana		pCMV-SPORT6
L0659	NCI_CGAP_Pan1		pancreas skin		pCMV-SPORT6
L0661	NCI_CGAP_Mel15	malignant melanoma,	SKIII	1	
		metastatic to		1	]
		lymph node			1
1.0662	NCI_CGAP_Gas4	poorly	stomach		pCMV-SPORT6
L0662	NCI_COAP_Gas4	differentiated	Stollinell		[ * ]
		adenocarcinoma			
		with signet r			
L0663	NCI_CGAP_Ut2	moderately-	uterus		pCMV-SPORT6
L0003	Nei_edai_etz	differentiated			'
		endometrial			
		adenocarcino			
L0664	NCI_CGAP_Ut3	poorly-	uterus		pCMV-SPORT6
Locot	1101_00111 _010	differentiated			ļ
		endometrial	1		
		adenocarcinoma,			
L0665	NCI_CGAP_Ut4	serous papillary	uterus		pCMV-SPORT6
		carcinoma, high			
		grade, 2 pooled t			
L0666	NCI_CGAP_Ut1	well-	uterus	1	pCMV-SPORT6
		differentiated		ì	İ
		endometrial			1
ŀ		adenocarcinoma,		1	1
		7	<del></del>		pCMV-SPORT6
L0667	NCI_CGAP_CML1	myeloid cells, 18	whole blood	l 1	pcMV-SPORTO
<u> </u>		pooled CML		1	
		cases, BCR/ABL		1	!
	11 1000	rearra	breast	MCF7	pCR II
L0669	Human MCF7 cDNA	breast adenocarcinoma	oreast	MCI'/	[Invitrogen]
	subtracted with MDA-	auenocaremonia	1	1	[
10004	MB-231 cDNA Stanley Frontal SB pool 1	frontal lobe (see	brain	<del>                                     </del>	pCR2.1-TOPO
L0684	Statiley Frontai SB pool 1	description)	""		(Invitrogen)
10605	Stanley Frontal SN pool 1	frontal lobe (see	brain		pCR2.1-TOPO
L0685	Stainey Fiolital Six pool I	description)	J		(Invitrogen)
10406	Stanley Frontal SN pool 2	frontal lobe (see	brain	1	pCR2.1-TOPO
L0686	Stanley Fibritian Siv poor 2	description)	J		(Invitrogen)
L0695	Human Glialblastoma Cell		Brain	BT-325	PCRII,
LUU93	Tunian Ghaibiastonia Cen				Invitrogen
L0697	Testis 1				PGEM 5zf(+)
L0698	Testis 2	<del>                                     </del>		<del>                                     </del>	PGEM 5zf(+)
L0700	Outward Alu-primed	+		1	pGEM-3Z
L0/00	hncDNA library	1			
L0717	Gessler Wilms tumor				pSPORT1
L0718					pSPORT1
L0718		<del>                                     </del>	uterus	<del>                                     </del>	pT7T3-Pac
LU/31	NbHPU				<u> </u>
L	INDHPU	<u> </u>		<del></del>	



	2NbHMSP	lesions	1 1 100	<u>-                                    </u>		(Pharmacia) with
	_ZINDRIVISP	lesions				a modified
1	٠					polylinker
						V_TYPE
L0757	Soares_senescent_fibrobla	senescent fibroblast				pT7T3D (Pharmacia) with
	sts_NbHSF	Holobiast				a modified
						polylinker
						V_TYPE
L0758	Soares_testis_NHT					pT7T3D-Pac
						(Pharmacia) with
						a modified polylinker
L0759	Soares_total_fetus_Nb2H					pT7T3D-Pac
	F8_9w			ŀ		(Pharmacia) with
	_					a modified
						polylinker
L0760	Barstead aorta HPLRB3	aorta				pT7T3D-Pac
l						(Pharmacia) with a modified
						polylinker
L0761	NCI_CGAP_CLL1	B-cell, chronic				pT7T3D-Pac
	<del>-</del>	lymphotic				(Pharmacia) with
		leukemia		1		a modified
1.0762	NCL CCAR R-1.1	breast				polylinker pT7T3D-Pac
L0762	NCI_CGAP_Br1.1	breast		ŀ		(Pharmacia) with
						a modified
						polylinker
L0763	NCI_CGAP_Br2	breast				pT7T3D-Pac
		•				(Pharmacia) with a modified
						polylinker
L0764	NCI_CGAP_Co3	colon				pT7T3D-Pac
	1101_00111 _000	501011	•	1		(Pharmacia) with
				1		a modified
10565	NG GOAD GA					polylinker
L0765	NCI_CGAP_Co4	colon				pT7T3D-Pac (Pharmacia) with
						a modified
]					;	polylinker
L0766	NCI_CGAP_GCB1	germinal center				pT7T3D-Pac
		B cell				(Pharmacia) with
			:			a modified polylinker
L0767	NCI_CGAP_GC3	pooled germ cell				pT7T3D-Pac
20,0,	Noi_een _ees	tumors				(Pharmacia) with
1						a modified
						polylinker
L0768	NCI_CGAP_GC4	pooled germ cell tumors				pT7T3D-Pac (Pharmacia) with
		tumors				a modified
						polylinker
L0769	NCI_CGAP_Bm25	anaplastic	brain		<u> </u>	pT7T3D-Pac
		oligodendroglio				(Pharmacia) with
		ma				a modified polylinker
L0770	NCI_CGAP_Brn23	glioblastoma	brain	<del>                                     </del>		pT7T3D-Pac
20,70	1.01_00/11 _DI1143	(pooled)	oimii			(Pharmacia) with
		, <del>-</del> /				a modified
						polylinker
L0771	NCI_CGAP_Co8	adenocarcinoma	colon		}	pT7T3D-Pac
						(Pharmacia) with a modified
						polylinker
L0772	NCI_CGAP_Co10	colon tumor	colon	1		pT7T3D-Pac
						. , - · - · - <del></del>

		RER+			(Pharmacia) with
•					a modified
					polylinker
L0773	NCI_CGAP_Co9	colon tumor	colon		pT7T3D-Pac
		RER+			(Pharmacia) with
					a modified
				ļ	polylinker
L0774	NCI_CGAP_Kid3		kidney		pT7T3D-Pac
					(Pharmacia) with
				l	a modified
					polylinker
L0775	NCI_CGAP_Kid5	2 pooled tumors	kidney		pT7T3D-Pac
		(clear cell type)			(Pharmacia) with
					a modified
70==	1101 0010 1				polylinker
L0776	NCI_CGAP_Lu5	carcinoid	lung	ŀ	pT7T3D-Pac
					(Pharmacia) with
					a modified
1.0333	C NITIME CI	D. J. H		<del>  </del>	polylinker
L0777	Soares_NhHMPu_S1	Pooled human	mixed (see		pT7T3D-Pac
		melanocyte, fetal	below)	1	(Pharmacia) with a modified
		heart, and			polylinker
1.0770	Comment of CDC C1	pregnant	1	<del> </del>	
L0779	Soares_NFL_T_GBC_S1	1	pooled		pT7T3D-Pac (Pharmacia) with
				[ I	a modified
					polylinker
L0780	Soares_NSF_F8_9W_OT		pooled		pT7T3D-Pac
LU/80	_PA_P_S1		pooled		(Pharmacia) with
	_FA_F_31			l	a modified
					polylinker
L0782	NCI_CGAP_Pr21	normal prostate	prostate	<del></del>	pT7T3D-Pac
L0702	Nei_eoai _i izi	normal prostate	prostate		(Pharmacia) with
					a modified
					polylinker
L0783	NCI_CGAP_Pr22	normal prostate	prostate		pT7T3D-Pac
20,00	1.01_00111_112	normal prosume	F	}	(Pharmacia) with
					a modified
					polylinker
L0784	NCI_CGAP_Lei2	leiomyosarcoma	soft tissue		pT7T3D-Pac
		'		1	(Pharmacia) with
				l	a modified
				<u> </u>	polylinker
L0785	Barstead spleen HPLRB2		spleen		pT7T3D-Pac
				<u> </u>	(Pharmacia) with
1	i				a modified
					polylinker
L0786	Soares_NbHFB		whole brain		pT7T3D-Pac
:		i			(Pharmacia) with
					a modified
7.00	NGL GO : D G : I			<b> </b>	polylinker
L0787	NCI_CGAP_Sub1			1 1	pT7T3D-Pac
	İ	1		<b> </b>	(Pharmacia) with
		1			a modified
1.0700	NOL COAR S 13			<del>                                     </del>	polylinker
L0788	NCI_CGAP_Sub2			]	pT7T3D-Pac
	1			]	(Pharmacia) with a modified
	1				polylinker
L0789	NCI_CGAP_Sub3			<del>  </del>	pT7T3D-Pac
LU/09	TACI_COMI_SU03				(Pharmacia) with
					a modified
				[ [	polylinker
L0790	NCI_CGAP_Sub4			<del> </del>	pT7T3D-Pac
] 20,70	1.01_00/11_0004				(Pharmacia) with
					a modified
					1

L0791				I I nolybnker
	NCI_CGAP_Sub5			polylinker pT7T3D-Pac
10/71	TICI_COAT_3003			(Pharmacia) with
				a modified
				polylinker
L0792	NCI_CGAP_Sub6			pT7T3D-Pac
				(Pharmacia) with
1				a modified
1.0702	NOL COAD O 17			polylinker
L0793	NCI_CGAP_Sub7			pT7T3D-Pac
1				(Pharmacia) with a modified
				polylinker
L0794	NCI_CGAP_GC6	pooled germ cell		pT7T3D-Pac
		tumors		(Pharmacia) with
] ]				a modified
				polylinker
L0796	NCI_CGAP_Brn50	medulloblastoma	brain	pT7T3D-Pac
				(Pharmacia) with
]				a modified
L0800	NCI_CGAP_Co16	colon tumor,	colon	polylinker pT7T3D-Pac
20000	HOZECOM ECOM	RER+	COIOII	(Pharmacia) with
i i	•	KEK!		a modified
				polylinker
L0803	NCI_CGAP_Kid11		kidney	pT7T3D-Pac
]				(Pharmacia) with
				a modified
7.0004	NOL COAD KIND	2 1 1	1 · 1	polylinker
L0804	NCI_CGAP_Kid12	2 pooled tumors (clear cell type)	kidney	pT7T3D-Pac (Pharmacia) with
		(Clear cen type)		a modified
1 1				polylinker
L0805	NCI_CGAP_Lu24	carcinoid	lung	pT7T3D-Pac
			•	(Pharmacia) with
1 1				a modified
10006	VO. 00 . D . 40			polylinker
L0806	NCI_CGAP_Lu19	squamous cell	lung	pT7T3D-Pac
		carcinoma, poorly	•	(Pharmacia) with a modified
		differentiated (4		polylinker
L0807	NCI_CGAP_Ov18	fibrotheoma	ovary	pT7T3D-Pac
1			0.2,	(Pharmacia) with
				a modified
				polylinker
	Barstead prostate BPH		prostate	pT7T3D-Pac
	HPLRB4 1			(Pharmacia) with
				a modified polylinker
L0809	NCI_CGAP_Pr28		prostate	pT7T3D-Pac
			prostate	(Pharmacia) with
1				a modified
				polylinker
L2251	Human fetal lung	Fetal lung		
L3904	NCI_CGAP_Brn64	glioblastoma with EGFR	brain	pCMV-SPORT6
		amplification		
L3905	NCI_CGAP_Brn67	anaplastic	brain	pCMV-SPORT6
~~~~		oligodendroglio	Jiani	
		ma with 1p/19q		
		loss		
L4497	NCI_CGAP_Br22	invasive ductal	breast	pCMV-SPORT6
		carcinoma, 3		
L4500	NOLOCAD IDUA	pooled samples		
1 143181 1	NCI_CGAP_HN16	moderate to	mouth	pAMP10
2-300		poorly		

	I	differentiated		
	1	invasive carcino		
L4501	NCI_CGAP_Sub8	mvasive earemo		pT7T3D-Pac (Pharmacia) with a modified polylinker
L4508	NCI_CGAP_Thy8	normal epithelium	thyroid	pAMP10
L4558	NCI_CGAP_Pan3		pancreas	pCMV-SPORT6
L4559	NCI_CGAP_Thy3	follicular carcinoma	thyroid	pCMV-SPORT6
L4747	NCI_CGAP_Brn41	oligodendroglio ma	brain	pT7T3D-Pac (Pharmacia) with a modified polylinker
L5564	NCI_CGAP_HN20		normal head/neck tissue	pAMP1
L5565	NCI_CGAP_Brn66	glioblastoma with probably TP53 mutation and witho	brain	pCMV-SPORT6
L5566	NCI_CGAP_Bm70	anaplastic oligodendroglio ma	brain	pCMV- SPORT6.ccdb
L5568	NCI_CGAP_HN21	nasopharyngeal carcinoma	head/neck	pAMP1
L5569	NCI_CGAP_HN17	normal epithelium	nasopharyn x	pAMP10
L5572	NCI_CGAP_Co27	adenocarcinoma (mucinous component)	colon	pAMP1
L5574	NCI_CGAP_HN19	normal epithelium	nasopharyn x	pAMP10
L5575	NCI_CGAP_Brn65	glioblastoma without EGFR amplification	brain	pCMV-SPORT6
L5622	NCI_CGAP_Skn3		skin	pCMV-SPORT6
L5623	NCI_CGAP_Skn4	squamous cell carcinoma	skin	pCMV-SPORT6

TABLE 5

OMIM	Description
Reference	
100690	Myasthenic syndrome, slow-channel congenital, 601462
100710	Myasthenic syndrome, slow-channel congenital, 601462
100730	Myasthenia gravis, neonatal transient
101000	Meningioma, NF2-related, sporadic Schwannoma, sporadic
101000	Neurofibromatosis, type 2
101000	Neurolemmomatosis
101000	Malignant mesothelioma, sporadic
102200	Somatotrophinoma

102700	Severe combined immunodeficiency due to ADA deficiency
102700	Hemolytic anemia due to ADA excess
	Autism, succinylpurinemic
103050	The state of the s
103050	Adenylosuccinase deficiency
103600	[Dysalbuminemic hyperthyroxinemia]
103600	[Dysalbuminemic hyperzincemia], 194470
103600	Analbuminemia
103850	Aldolase A deficiency
103950	Emphysema due to alpha-2-macroglobulin deficiency
104150	[AFP deficiency, congenital]
104150	[Hereditary persistence of alpha-fetoprotein]
104311	Alzheimer disease-3
104500	Amelogenesis imperfecta-2, hypoplastic local type
104770	Amyloidosis, secondary, susceptibility to
106100	Angioedema, hereditary
106150	Hypertension, essential, susceptibility to
106150	Preeclampsia, susceptibility to
106300	Ankylosing spondylitis
107250	Anterior segment mesenchymal dysgenesis
107670	Apolipoprotein A-II deficiency
107741	Hyperlipoproteinemia, type III
107777	Diabetes insipidus, nephrogenic, autosomal recessive, 222000
108725	Atherosclerosis, susceptibility to
108800	Atrial septal defect, secundum type
109150	Machado-Joseph disease
109270	Renal tubular acidosis, distal, 179800
109270	Spherocytosis, hereditary
109270	[Acanthocytosis, one form]
109270	[Elliptocytosis, Malaysian-Melanesian type]
109270	Hemolytic anemia due to band 3 defect
110700	Vivax malaria, susceptibility to
112410	Hypertension with brachydactyly
113900	Heart block, progressive familial, type I
114290	Campomelic dysplasia with autosomal sex reversal
114835	Monocyte carbox yesterase deficiency
115665	Cataract, congenital, Volkmann type
116800	Cataract, Marner type
116860	Cavernous angiomatous malformations
118210	Charcot-Marie-Tooth neuropathy-2A
118485	Polycystic ovary syndrome with hyperandrogenemia
118800	Choreoathetosis, familial paroxysmal
120070	Alport syndrome, autosomal recessive, 203780
120110	Metaphyseal chondrodysplasia, Schmid type
120131	Alport syndrome, autosomal recessive, 203780
120131	Hematuria, familial benign
120140	Osteoarthrosis, precocious
120110	1 Control of the cont

120140	SED congenita
120140	SMED Strudwick type
120140	Stickler syndrome, type I
120140	Wagner syndrome, type II
120140	Achondrogenesis-hypochondrogenesis, type II
120140	Kniest dysplasia
120150	Osteogenesis imperfecta, 4 clinical forms, 166200, 166210,
	259420, 166220
120150	Osteoporosis, idiopathic, 166710
120150	Ehlers-Danlos syndrome, type VIIA1, 130060
120260	Epiphyseal dysplasia, multiple, type 2, 600204
120290	OSMED syndrome, 215150
120290	Stickler syndrome, type II, 184840
120550	C1q deficiency, type A
120570	C1q deficiency, type B
120575	C1q deficiency, type C
120700	C3 deficiency
120810	C4 deficiency
120820	C4 deficiency
121014	Heterotaxia, visceroatrial, autosomal recessive
121800	Corneal dystrophy, crystalline, Schnyder
122720	Nicotine addiction, protection from
122720	Coumarin resistance, 122700
123000	Craniometaphyseal dysplasia
123101	Craniosynostosis, type 2
123270	[Creatine kinase, brain type, ectopic expression of]
123620	Cataract, cerulean, type 2, 601547
123660	Cataract, Coppock-like
123940	White sponge nevus, 193900
124030	Parkinsonism, susceptibility to
124030	Debrisoquine sensitivity
125660	Myopathy, desminopathic
125660	Cardiomyopathy
125852	Insulin-dependent diabetes mellitus-2
126337	Myxoid liposarcoma
126340	Xeroderma pigmentosum, group D, 278730
126391	DNA ligase I deficiency
126451	Schizophrenia, susceptibility to
126452	Autonomic nervous system dysfunction
126452	[Novelty seeking personality]
126600	Drusen, radial, autosomal dominant
126650	Chloride diarrhea, congenital, Finnish type, 214700
126650	Colon cancer
129900	EEC syndrome-1
130410	Glutaricaciduria, type IIB
130500	Elliptocytosis-1
130650	Beckwith-Wiedemann syndrome
	1 2 TOTAL TOTAL STATE OF THE ST

131100	Multiple endocrine neoplasia I
131100	Prolactinoma, hyperparathyroidism, carcinoid syndrome
131100	Carcinoid tumor of lung
131400	Eosinophilia, familial
133171	[Erythrocytosis, familial], 133100
133200	Erythrokeratodermia variabilis
133450	Neuroepithelioma
133450	Ewing sarcoma
133701	Exostoses, multiple, type 2
133780	Vitreoretinopathy, exudative, familial
134580	Factor XIIIB deficiency
134790	Hyperferritinemia-cataract syndrome, 600886
134820	Dysfibrinogenemia, alpha type, causing bleeding diathesis
134820	Dysfibrinogenemia, alpha type, causing recurrent thrombosis
134820	Amyloidosis, hereditary renal, 105200
134830	Dysfibrinogenemia, beta type
134850	Dysfibrinogenemia, gamma type
134850	Hypofibrinogenemia, gamma type
135600	Ehlers-Danlos syndrome, type X
135700	Fibrosis of extraocular muscles, congenital, 1
135940	Ichthyosis vulgaris, 146700
136435	Ovarian dysgenesis, hypergonadotropic, with normal karyotype,
130433	233300
136836	Fucosyltransferase-6 deficiency
138030	[Hyperproglucagonemia]
138033	Diabetes mellitus, type II
138079	Hyperinsulinism, familial, 602485
138079	MODY, type 2, 125851
138130	Hyperinsulinism-hyperammonemia syndrome
138140	Glucose transport defect, blood-brain barrier
138190	Diabetes mellitus, noninsulin-dependent
138570	Non-insulin dependent diabetes mellitus, susceptibility to
138720	Bernard-Soulier syndrome, type B
138981	Pulmonary alveolar proteinosis, 265120
139350	Epidermolytic hyperkeratosis, 113800
139350	Keratoderma, palmoplantar, nonepidermolytic
140100	[Anhaptoglobinemia]
140100	[Hypohaptogloginemia]
141900	Methemoglobinemias, beta-
141900	Sickle cell anemia
141900	Thalassemias, beta-
141900	Erythremias, beta-
141900	HPFH, deletion type
141900	Heinz body anemias, beta-
142000	Thalassemia due to Hb Lepore
142000	Thalassemia, delta-
142000	HPFH, nondeletion type A
142200	TH TH, nondeletion type II

142250	HPFH, nondeletion type G
142270	Hereditary persistence of fetal hemoglobin
142857	Pemphigoid, susceptibility to
142858	Beryllium disease, chronic, susceptibility to
142989	Synpolydactyly, type II, 186000
143890	Hypercholesterolemia, familial
145001	Hyperparathyroidism-jaw tumor syndrome
145260	Pseudohypoaldosteronism, type II
145410	Opitz G syndrome, type II
145981	Hypocalciuric hypercalcemia, type II
146760	[IgG receptor I, phagocytic, familial deficiency of]
146790	Lupus nephritis, susceptibility to
147050	Atopy
147061	Allergy and asthma susceptibility
147141	Leukemia, acute lymphoblastic
147200	[Kappa light chain deficiency]
147545	Diabetes mellitus, noninsulin-dependent
147575	Myelodysplastic syndrome, preleukemic
147575	Myelogenous leukemia, acute
147575	Macrocytic anemia refractory, of 5q- syndrome, 153550
147670	Rabson-Mendenhall syndrome
147670	Diabetes mellitus, insulin-resistant, with acanthosis nigricans
147670	Leprechaunism
148040	Epidermolysis bullosa simplex, Koebner, Dowling-Meara, and Weber-Cockayne types, 131900, 131760, 131800
148041	Pachyonychia congenita, Jadassohn-Lewandowsky type, 167200
148043	Meesmann corneal dystrophy, 122100
148065	White sponge nevus, 193900
148070	Liver disease, susceptibility to, from hepatotoxins or viruses
148080	Epidermolytic hyperkeratosis, 113800
148370	Keratolytic winter erythema
150000	Exertional myoglobinuria due to deficiency of LDH-A
150250	Larsen syndrome, autosomal dominant
150270	Laryngeal adductor paralysis
150292	Epidermolysis bullosa, Herlitz junctional type, 226700
151410	Leukemia, chronic myeloid
151440	Leukemia, T-cell acute lymphoblastoid
151670	Hepatic lipase deficiency
152445	Vohwinkel syndrome, 124500
152445	Erythrokeratoderma, progressive symmetric, 602036
152760	Hypogonadotropic hypogonadism due to GNRH deficiency, 227200
153454	Ehlers-Danlos syndrome, type VI, 225400
153455	Cutis laxa, recessive, type I, 219100
153700	Macular dystrophy, vitelliform type
154275	Malignant hyperthermia susceptibility 2

154076	DATE (1 d)
154276	Malignant hyperthermia susceptibility 3
154705	Marfan syndrome, type II
155600	Malignant melanoma, cutaneous
156225	Muscular dystrophy, congenital merosin-deficient
156232	Mesomelic dysplasia, Kantaputra type
156845	Tietz syndrome, 103500
156845	Waardenburg syndrome, type IIA, 193510
156845	Waardenburg syndrome/ocular albinism, digenic, 103470
157147	Abetalipoproteinemia, 200100
157640	PEO with mitochondrial DNA deletions, type 1
157655	Lactic acidosis due to defect in iron-sulfur cluster of complex I
159000	Muscular dystrophy, limb-girdle, type 1A
159001	Muscular dystrophy, limb-girdle, type 1B
160900	Myotonic dystrophy
161015	Mitochondrial complex I deficiency, 252010
162100	Neuralgic amyotrophy with predilection for brachial plexus
164009	Leukemia, acute promyelocytic, NUMA/RARA type
164040	Leukemia, acute promyelocytic, NPM/RARA type
164200	Oculodentodigital dysplasia
164200	Syndactyly, type III, 186100
164500	Spinocerebellar ataxia-7
164731	Ovarian carcinoma, 167000
164920	Piebaldism
164920	Mast cell leukemia
164920	Mastocytosis with associated hematologic disorder
164953	Liposarcoma
165240	Pallister-Hall syndrome, 146510
165240	Postaxial polydactyly type A1, 174200
165240	Greig cephalopolysyndactyly syndrome, 175700
167250	Paget disease of bone
167410	Rhabdomyosarcoma, alveolar, 268220
168360	Paraneoplastic sensory neuropathy
168461	Multiple myeloma, 254250
168461	Parathyroid adenomatosis 1
168461	Centrocytic lymphoma
168470	Humoral hypercalcemia of malignancy
168500	Parietal foramina
170261	Bare lymphocyte syndrome, type I, due to TAP2 deficiency
170500	Myotonia congenita, atypical acetazolamide-responsive
170500	Paramyotonia congenita, 168300
170500	Hyperkalemic periodic paralysis
170650	Periodontitis, juvenile
171190	Hypertension, essential, 145500
171650	Lysosomal acid phosphatase deficiency
171760	Hypophosphatasia, adult, 146300
171760	Hypophosphatasia, infantile, 241500
	1 1 2 2

172400	
172400	Hemolytic anemia due to glucosephosphate isomerase deficiency
172400	
172430	Hydrops fetalis, one form Enolase deficiency
173360	
173360	Thrombophilia due to excessive plasminogen activator inhibitor
173850	Hemorrhagic diathesis due to PAI1 deficiency
173870	Polio, susceptibility to
173870	Xeroderma pigmentosum Fanconi anemia
173910	Polycystic kidney disease, adult, type II
174000	Medullary cystic kidney disease, AD
174900	Polyposis, juvenile intestinal
176100	Porphyria cutanea tarda
176100	Porphyria, hepatoerythropoietic
176730	Diabetes mellitus, rare form
176730	Hyperproinsulinemia, familial
176730	MODY, one form
176930	Dysprothrombinemia
176930	Hypoprothrombinemia
176943	Apert syndrome, 101200
176943	Pfeiffer syndrome, 101600
176943	Beare-Stevenson cutis gyrata syndrome, 123790
176943	Crouzon craniofacial dysostosis, 123500
176943	Jackson-Weiss syndrome, 123150
177070	Spherocytosis, hereditary, Japanese type
177070	Hermansky-Pudlak syndrome, 203300
177900	Psoriasis susceptibility-1
178300	Ptosis, hereditary congenital, 1
178600	Pulmonary hypertension, familial primary
178640	Pulmonary alveolar proteinosis, congenital, 265120
179450	Ragweed sensitivity
179755	Renal cell carcinoma, papillary, 1
180071	Retinitis pigmentosa, autosomal recessive
180100	Retinitis pigmentosa-1
180104	Retinitis pigmentosa-9
180105	Retinitis pigmentosa-10
180721	Retinitis pigmentosa, digenic
180840	Susceptibility to IDDM
180860	Russell-Silver syndrome
180901	Malignant hyperthermia susceptibility 1, 145600
180901	Central core disease, 117000
181405	Scapuloperoneal spinal muscular atrophy, New England type
181430	Scapuloperoneal syndrome, myopathic type
181460	Schistosoma mansoni, susceptibility/resistance to
181600	Sclerotylosis
182280	Small-cell cancer of lung
182380	Glucose/galactose malabsorption

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182500	Cataract, congenital
182600	Spastic paraplegia-3A
182860	Pyropoikilocytosis
182860	Spherocytosis, recessive
182860	Elliptocytosis-2
185430	Atherosclerosis, susceptibility to
185470	Myopathy due to succinate dehydrogenase deficiency
185800	Symphalangism, proximal
186860	Leukemia/lymphoma, T-cell
188070	Bleeding disorder due to defective thromboxane A2 receptor
188826	Sorsby fundus dystrophy, 136900
189800	Preeclampsia/eclampsia
190020	Bladder cancer, 109800
190040	Meningioma, SIS-related
190040	Dermatofibrosarcoma protuberans
190040	Giant-cell fibroblastoma
190160	Thyroid hormone resistance, 274300, 188570
190900	Colorblindness, tritan
191010	Cardiomyopathy, familial hypertrophic, 3, 115196
191044	Cardiomyopathy, familial hypertrophic
191170	Colorectal cancer, 114500
191170	Li-Fraumeni syndrome
191181	Cervical carcinoma
191290	Segawa syndrome, recessive
191315	Insensitivity to pain, congenital, with anhidrosis, 256800
192090	Ovarian carcinoma
192090	Breast cancer, lobular
192090	Endometrial carcinoma
192090	Gastric cancer, familial, 137215
192500	Jervell and Lange-Nielsen syndrome, 220400
192500	Long QT syndrome-1
193235	Vitreoretinopathy, neovascular inflammatory
193500	Rhabdomyosarcoma, alveolar, 268220
193500	Waardenburg syndrome, type I
193500	Waardenburg syndrome, type III, 148820
193500	Craniofacial-deafness-hand syndrome, 122880
194071	Wilms tumor, type 2
194071	Adrenocortical carcinoma, hereditary, 202300
200990	Acrocallosal syndrome
201460	Acyl-CoA dehydrogenase, long chain, deficiency of
201910	Adrenal hyperplasia, congenital, due to 21-hydroxylase
	deficiency
203100	Waardenburg syndrome/ocular albinism, digenic, 103470
203100	Albinism, oculocutaneous, type IA
203300	Hermansky-Pudlak syndrome
203740	Alpha-ketoglutarate dehydrogenase deficiency
203800	Alstrom syndrome

204500	
204500	Ceroid-lipofuscinosis, neuronal 2, classic late infantile
205100	Amyotrophic lateral sclerosis, juvenile
207750	Hyperlipoproteinemia, type Ib
208100	Arthrogryposis multiplex congenita, neurogenic
208250	Jacobs syndrome
209901	Bardet-Biedl syndrome 1
211420	Breast cancer, ductal
216900	Achromatopsia
217000	C2 deficiency
218000	Andermann syndrome
219800	Cystinosis, nephropathic
221770	Polycystic lipomembranous osteodysplasia with sclerosing
	leukencephalopathy
221820	Gliosis, familial progressive subcortical
222100	Diabetes mellitus, insulin-dependent-1
222800	Hemolytic anemia due to bisphosphoglycerate mutase
	deficiency
227220	[Eye color, brown]
227646	Fanconi anemia, type D
230000	Fucosidosis
230350	Galactose epimerase deficiency
230800	Gaucher disease
230800	Gaucher disease with cardiovascular calcification
231550	Achalasia-addisonianism-alacrimia syndrome
231670	Glutaricaciduria, type I
231680	Glutaricaciduria, type IIA
231950	Glutathioninuria
232600	McArdle disease
232800	Glycogen storage disease VII
233100	[Renal glucosuria]
233700	Chronic granulomatous disease due to deficiency of NCF-1
235200	Hemochromatosis
236730	Urofacial syndrome
237300	Carbamoylphosphate synthetase I deficiency
238600	Chylomicronemia syndrome, familial
238600	Combined hyperlipemia, familial
238600	Hyperlipoproteinemia I
238600	Lipoprotein lipase deficiency
239500	Hyperprolinemia, type I
243500	Isovalericacidemia
245000	Papillon-Lefevre syndrome
245200	Krabbe disease
245900	Norum disease
245900	Fish-eye disease
246450	HMG-CoA lyase deficiency
246530	Leukotriene C4 synthase deficiency
246900	Lipoamide dehydrogenase deficiency
4 1 0700	Lipoannue denydrogenase denciency

Mannosidosis, beta-
Maple syrup urine disease, type Ia
Maple syrup urine disease, type Ib
Meckel syndrome
Microphthalmia, autosomal recessive
Mucolipidosis II
Mucolipidosis III
Mulibrey nanism
Myasthenia gravis, familial infantile
Schwartz-Jampel syndrome
Sialidosis, type I
Sialidosis, type II
Neuroblastoma
Niemann-Pick disease, type A
Niemann-Pick disease, type B
3-methylglutaconicaciduria, type III
Gyrate atrophy of choroid and retina with ornithinemia, B6
responsive or unresponsive
Osteopetrosis, recessive
Osteoporosis-pseudoglioma syndrome
Hyperoxaluria, primary, type 1
Pseudo-Zellweger syndrome
Myopathy due to phosphoglycerate mutase deficiency
Bjornstad syndrome
Porphyria, congenital erythropoietic
Adrenoleukodystrophy, pseudoneonatal
Anemia, hemolytic, due to PK deficiency
[Hair color, red]
Situs inversus viscerum
Canavan disease
GM2-gangliosidosis, AB variant
Tay-Sachs disease
[Hex A pseudodeficiency]
GM2-gangliosidosis, juvenile, adult
Thromboxane synthase deficiency
Transcobalamin II deficiency
Tyrosinemia, type II
Tyrosinemia, type I
Usher syndrome, type 1A
Usher syndrome, type 2
Wernicke-Korsakoff syndrome, susceptibility to
Wrinkly skin syndrome
Nephrolithiasis, type I, 310468
Proteinuria, low molecular weight, with hypercalciuric
nephrocalcinosis
Dent disease, 300009
Hypophosphatemia, type III

300031	Mental retardation, X-linked, FRAXF type
300044	Wernicke-Korsakoff syndrome, susceptibility to
300046	Mental retardation, X-linked 23, nonspecific
300047	Mental retardation, X-linked 20
300048	Intestinal pseudoobstruction, neuronal, X-linked
300049	Nodular heterotopia, bilateral periventricular
300049	BPNH/MR syndrome
300055	Mental retardation with psychosis, pyramidal signs, and
	macroorchidism
300088	Epilepsy, female restricted, with mental retardation
300100	Adrenoleukodystrophy
300100	Adrenomyeloneuropathy
300104	Mental retardation, X-linked nonspecific, 309541
300123	Mental retardation with isolated growth hormone deficiency
300126	Dyskeratosis congenita-1, 305000
300300	XLA and isolated growth hormone deficiency, 307200
300300	Agammaglobulinemia, type 1, X-linked
301000	Thrombocytopenia, X-linked, 313900
301000	Wiskott-Aldrich syndrome
301201	Amelogenesis imperfecta-3, hypoplastic type
301300	Anemia, sideroblastic/hypochromic
301500	Fabry disease
301590	Anophthalmos-1
301830	Arthrogryposis, X-linked (spinal muscular atrophy, infantile, X-
301830	linked)
301835	Arts syndrome
301845	Bazex syndrome
301900	Borjeson-Forssman-Lehmann syndrome
302060	Noncompaction of left ventricular myocardium, isolated
302060	Barth syndrome
302060	Cardiomyopathy, X-linked dilated, 300069
302060	Endocardial fibroelastosis-2
-	
302960 303400	Chondrodysplasia punctata, X-linked dominant Cleft palate, X-linked
303630 303630	Alport syndrome, 301050
	Leiomyomatosis diffuse with Alport syndrome
303631	Leiomyomatosis, diffuse, with Alport syndrome
303700	Colorblindness, blue monochromatic
303800	Colorblindness, deutan
303900	Colorblindness, protan
304340	Mental retardation, X-linked, syndromic-5, with Dandy-Walker
20.4500	malformation, basal ganglia disease, and seizures
304500	Deafness, X-linked 2, perceptive congenital
304700	Mohr-Tranebjaerg syndrome
304700	Deafness, X-linked 1, progressive
304700	Jensen syndrome, 311150
304800	Diabetes insipidus, nephrogenic

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305400	Aarskog-Scott syndrome
305450	FG syndrome
305900	Favism
305900	G6PD deficiency
305900	Hemolytic anemia due to G6PD deficiency
306700	Hemophilia A
306900	Hemophilia B
306995	[Homosexuality, male]
307150	Hypertrichosis, congenital generalized
307700	Hypoparathyroidism, X-linked
308000	HPRT-related gout
308000	Lesch-Nyhan syndrome
308300	Incontinentia pigmenti, sporadic type
308310	Incontinentia pigmenti, familial
308840	Spastic paraplegia, 312900
308840	Hydrocephalus due to aqueductal stenosis, 307000
308840	MASA syndrome, 303350
309000	Lowe syndrome
309200	Manic-depressive illness, X-linked
309300	Megalocornea, X-linked
309470	Mental retardation, X-linked, syndromic-3, with spastic diplegia
309500	Renpenning syndrome-1
309548	Mental retardation, X-linked, FRAXE type
309605	Mental retardation, X-linked, syndromic-4, with congenital
	contractures and low fingertip arches
309610	Mental retardation, X-linked, syndromic-2, with dysmorphism
	and cerebral atrophy
309620	Mental retardation-skeletal dysplasia
309900	Mucopolysaccharidosis II
310300	Emery-Dreifuss muscular dystrophy
310400	Myotubular myopathy, X-linked
310460	Myopia-1
310460	Bornholm eye disease
310490	Cowchock syndrome
311050	Optic atrophy, X-linked
311300	Otopalatodigital syndrome, type I
311510	Waisman parkinsonism-mental retardation syndrome
311850	Phosphoribosyl pyrophosphate synthetase-related gout
312080	Pelizaeus-Merzbacher disease
312080	Spastic paraplegia-2, 312920
313850	Thoracoabdominal syndrome
314300	Goeminne TKCR syndrome
314400	Cardiac valvular dysplasia-1
600040	Colorectal cancer
600045	Xeroderma pigmentosum, group E, subtype 2
600079	Colon cancer
600105	Retinitis pigmentosa-12, autosomal recessive

600119	Muscular dystrophy, Duchenne-like, type 2
600119	Adhalinopathy, primary
600138	Retinitis pigmentosa-11
600143	Epilepsy, progressive, with mental retardation
600151	Bardet-Biedl syndrome 3
600163	Long QT syndrome-3
600179	Leber congenital amaurosis, type I, 204000
600194	Ichthyosis bullosa of Siemens, 146800
600202	Dyslexia, specific, 2
600223	Spinocerebellar ataxia-4
600231	Palmoplantar keratoderma, Bothnia type
600258	Colorectal cancer, hereditary nonpolyposis, type 3
600261	Ehlers-Danlos-like syndrome
600266	Resistance/susceptibility to TB, etc.
600276	Cerebral arteriopathy with subcortical infarcts and
	leukoencephalopathy, 125310
600281	Non-insulin-dependent diabetes mellitus, 125853
600281	MODY, type 1, 125850
600319	Diabetes mellitus, insulin-dependent, 4
600332	Rippling muscle disease-1
600512	Epilepsy, partial
600525	Trichodontoosseous syndrome, 190320
600528	CPT deficiency, hepatic, type I, 255120
600536	Myopathy, congenital
600623	Prostate cancer, 176807
600759	Alzheimer disease-4
600807	Bronchial asthma
600808	Enuresis, nocturnal, 2
600811	Xeroderma pigmentosum, group E, DDB-negative subtype, 278740
600839	Bartter syndrome, 241200
600850	Schizophrenia disorder-4
600856	Beckwith-Wiedemann syndrome, 130650
600882	Charcot-Marie-Tooth neuropathy-2B
600897	Cataract, zonular pulverulent-1, 116200
600900	Muscular dystrophy, limb-girdle, type 2E
600918	Cystinuria, type III
600956	Persistent Mullerian duct syndrome, type II, 261550
600957	Persistent Mullerian duct syndrome, type I, 261550
600958	Cardiomyopathy, familial hypertrophic, 4, 115197
600971	Deafness, autosomal recessive 6
600975	Glaucoma 3, primary infantile, B
600977	Cone dystrophy, progressive
600995	Nephrotic syndrome, idiopathic, steroid-resistant
600996	Arrhythmogenic right ventricular dysplasia-2
601105	Pycnodysostosis, 265800
601154	Cardiomyopathy, dilated, 1E
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601202	Cataract, anterior polar-2
601208	Insulin-dependent diabetes mellitus-11
601226	Progressive external ophthalmoplegia, type 2
601238	Cerebellar ataxia, Cayman type
601277	Ichthyosis, lamellar, type 2
601284	Hereditary hemorrhagic telangiectasia-2, 600376
601318	Diabetes mellitus, insulin-dependent, 13
601385	Prostate cancer
601410	Diabetes mellitus, transient neonatal
601412	Deafness, autosomal dominant 7
601458	Inflammatory bowel disease-2
601596	Charcot-Marie-Tooth neuropathy, demyelinating
601649	Blepharophimosis, epicanthus inversus, and ptosis, type 2
601650	Paraganglioma, familial nonchromaffin, 2
601652	Glaucoma 1A, primary open angle, juvenile-onset, 137750
601666	Insulin-dependent diabetes mellitus-15
601669	Hirschsprung disease, one form
601680	Distal arthrogryposis, type 2B
601728	Bannayan-Zonana syndrome, 153480
601728	Cowden disease, 158350
601728	Endometrial carcinoma
601728	Lhermitte-Duclos syndrome
601744	Systemic lupus erythematosus, susceptibility to, 1
601757	Rhizomelic chondrodysplasia punctata, type 1, 215100
601769	Osteoporosis, involutional
601769	Rickets, vitamin D-resistant, 277440
601777	Cone dystrophy, progressive
601780	Ceroid-lipofuscinosis, neuronal-6, variant late infantile
601800	[Hair color, brown]
601843	Hypothyroidism, congenital, 274400
601844	Pseudohypoaldosteronism type II
601846	Muscular dystrophy with rimmed vacuoles
601863	Bare lymphocyte syndrome, complementation group C
601868	Deafness, autosomal dominant 13
601884	[High bone mass]
601928	Monilethrix, 158000
601969	Medulloblastoma, 155255
601969	Glioblastoma multiforme, 137800
601975	Ectodermal dysplasia/skin fragility syndrome
601990	Neuroblastoma
602023	Bartter syndrome, type 3
602025	Obesity/hyperinsulinism, susceptibility to
602084	Endometrial carcinoma
602089	Hemangioma, capillary, hereditary
602096	Alzheimer disease-5
602116	Glioma
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602136	Refsum disease, infantile, 266510
602136	Zellweger syndrome-1, 214100
602136	Adrenoleukodystrophy, neonatal, 202370
602153	Monilethrix, 158000
602216	Peutz-Jeghers syndrome, 175200
602225	Cone-rod retinal dystrophy-2, 120970
602225	Leber congenital amaurosis, type III
602280	Retinitis pigmentosa-14, 600132
602447	Coronary artery disease, susceptibility to
602475	Ossification of posterior longitudinal ligament of spine
602477	Febrile convulsions, familial, 2
602491	Hyperlipidemia, familial combined, 1
602568	Homocystinuria-megaloblastic anemia, cbl E type, 236270
602629	Dystonia-6, torsion
602631	Rhabdomyosarcoma, 268210
602631	Breast Cancer
602685	Mental retardation, severe, with spasticity and tapetoretinal
1	degeneration
602716	Nephrosis-1, congenital, Finnish type, 256300
602771	Muscular dystrophy, congenital, with early spine rigidity
602772	Retinitis pitmentosa-24

Mature Polypeptides

The present invention also encompasses mature forms of a polypeptide having [161] the amino acid sequence of SEQ ID NO:Y and/or the amino acid sequence encoded by the cDNA in a deposited clone. Polynucleotides encoding the mature forms (such as, for example, the polynucleotide sequence in SEQ ID NO:X and/or the polynucleotide sequence contained in the cDNA of a deposited clone) are also encompassed by the invention. Moreover, fragments or variants of these polypeptides (such as, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to these polypeptides, or polypeptides encoded by a polynucleotide that hybridizes under stringent conditions to the complementary strand of the polynucleotide encoding these polypeptides) are also encompassed by the invention. In preferred embodiments, these fragments or variants retain one or more functional acitivities of the full-length or mature form of the polypeptide (e.g., biological activity, antigenicity [ability to bind (or compete with a polypeptide of the invention for binding) to an anti-polypeptide of the invention antibody], immunogenicity (ability to generate antibody which binds to a specific polypeptide of the invention), ability to form multimers with polypeptides of the invention, and ability to bind to a receptor or ligand for a polypeptide of the invention). Antibodies that bind the polypeptides of the invention, and polynucleotides encoding these polypeptides are also encompassed by the invention.

According to the signal hypothesis, proteins secreted by mammalian cells have a signal or secretary leader sequence which is cleaved from the mature protein once export of the growing protein chain across the rough endoplasmic reticulum has been initiated. Most mammalian cells and even insect cells cleave secreted proteins with the same specificity. However, in some cases, cleavage of a secreted protein is not entirely uniform, which results in two or more mature species of the protein. Further, it has long been known that cleavage specificity of a secreted protein is ultimately determined by the primary structure of the complete protein, that is, it is inherent in the amino acid sequence of the polypeptide.

[163] Methods for predicting whether a protein has a signal sequence, as well as the cleavage point for that sequence, are available. For instance, the method of McGeoch, Virus Res. 3:271-286 (1985), uses the information from a short N-terminal charged region and a subsequent uncharged region of the complete (uncleaved) protein. The method of von Heinje, Nucleic Acids Res. 14:4683-4690 (1986) uses the information from the residues surrounding the cleavage site, typically residues -13 to +2, where +1 indicates the amino terminus of the secreted protein. The accuracy of predicting the cleavage points of known mammalian secretory proteins for each of these methods is in the range of 75-80%. (von Heinje, supra.) However, the two methods do not always produce the same predicted cleavage point(s) for a given protein.

In the present case, the deduced amino acid sequence of the secreted polypeptide was analyzed by a computer program called SignalP (Henrik Nielsen et al., Protein Engineering 10:1-6 (1997)), which predicts the cellular location of a protein based on the amino acid sequence. As part of this computational prediction of localization, the methods of McGeoch and von Heinje are incorporated. The analysis of the amino acid sequences of the secreted proteins described herein by this program provided the results shown in Table 1A.

In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, the predicted mature form of the polypeptide as delineated in columns 14 and 15 of Table 1A. Moreover, fragments or variants of these polypeptides (such as, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to these polypeptides, or polypeptides encoded by a polynucleotide that hybridizes under stringent conditions to the complementary strand of the polynucleotide encoding these polypeptides) are also encompassed by the invention. In preferred

embodiments, these fragments or variants retain one or more functional acitivities of the full-length or mature form of the polypeptide (e.g., biological activity, antigenicity [ability to bind (or compete with a polypeptide of the invention for binding) to an anti-polypeptide of the invention antibody], immunogenicity (ability to generate antibody which binds to a specific polypeptide of the invention), ability to form multimers with polypeptides of the invention, and ability to bind to a receptor or ligand for a polypeptide of the invention). Antibodies that bind the polypeptides of the invention, and polynucleotides encoding these polypeptides are also encompassed by the invention.

[166] Polynucleotides encoding proteins comprising, or consisting of, the predicted mature form of polypeptides of the invention (e.g., polynucleotides having the sequence of SEQ ID NO: X (Table 1A, column 4), the sequence delineated in columns 7 and 8 of Table 1A, and a sequence encoding the mature polypeptide delineated in columns 14 and 15 of Table 1A (e.g., the sequence of SEQ ID NO:X encoding the mature polypeptide delineated in columns 14 and 15 of Table 1)) are also encompassed by the invention, as are fragments or variants of these polynucleotides (such as, fragments as described herein, polynucleotides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to these polynucleotides, and nucleic acids which hybridizes under stringent conditions to the complementary strand of the polynucleotide).

As one of ordinary skill would appreciate, however, cleavage sites sometimes vary from organism to organism and cannot be predicted with absolute certainty. Accordingly, the present invention provides secreted polypeptides having a sequence shown in SEQ ID NO:Y which have an N-terminus beginning within 15 residues of the predicted cleavage point (i.e., having 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15 more or less contiguous residues of SEQ ID NO:Y at the N-terminus when compared to the predicted mature form of the polypeptide (e.g., the mature polypeptide delineated in columns 14 and 15 of Table 1). Similarly, it is also recognized that in some cases, cleavage of the signal sequence from a secreted protein is not entirely uniform, resulting in more than one secreted species. These polypeptides, and the polynucleotides encoding such polypeptides, are contemplated by the present invention.

[168] Moreover, the signal sequence identified by the above analysis may not necessarily predict the naturally occurring signal sequence. For example, the naturally occurring signal sequence may be further upstream from the predicted signal sequence. However, it is likely that the predicted signal sequence will be capable of directing the secreted protein to the ER. Nonetheless, the present invention provides the mature protein

produced by expression of the polynucleotide sequence of SEQ ID NO:X and/or the polynucleotide sequence contained in the cDNA of a deposited clone, in a mammalian cell (e.g., COS cells, as desribed below). These polypeptides, and the polynucleotides encoding such polypeptides, are contemplated by the present invention.

Polynucleotide and Polypeptide Variants

[169] The present invention is also directed to variants of the polynucleotide sequence disclosed in SEQ ID NO:X or the complementary strand thereto, nucleotide sequences encoding the polypeptide of SEQ ID NO:Y, the nucleotide sequence of SEQ ID NO:X that encodes the polypeptide sequence as defined in columns 13 and 14 of Table 1A, nucleotide sequences encoding the polypeptide sequence as defined in columns 13 and 14 of Table 1A, the nucleotide sequence of SEQ ID NO:X encoding the polypeptide sequence as defined in column 7 of Table 1B, nucleotide sequences encoding the polypeptide as defined in column 7 of Table 1B, the nucleotide sequence as defined in columns 8 and 9 of Table 2, nucleotide sequences encoding the polypeptide encoded by the nucleotide sequence as defined in columns 8 and 9 of Table 2, the nucleotide sequence as defined in column 6 of Table 1C, nucleotide sequences encoding the polypeptide encoded by the nucleotide sequence as defined in column 6 of Table 1C, the cDNA sequence contained in Clone ID NO:Z, nucleotide sequences encoding the polypeptide encoded by the cDNA sequence contained in Clone ID NO:Z, and/or nucleotide sequences encoding a mature (secreted) polypeptide encoded by the cDNA sequence contained in Clone ID NO:Z.

[170] The present invention also encompasses variants of the polypeptide sequence disclosed in SEQ ID NO:Y, the polypeptide as defined in columns 13 and 14 of Table 1A, the polypeptide sequence as defined in column 7 of Table 1B, a polypeptide sequence encoded by the polynucleotide sequence in SEQ ID NO:X, a polypeptide sequence encoded by the nucleotide sequence as defined in columns 8 and 9 of Table 2, a polypeptide sequence encoded by the nucleotide sequence as defined in column 6 of Table 1C, a polypeptide sequence encoded by the complement of the polynucleotide sequence in SEQ ID NO:X, the polypeptide sequence encoded by the cDNA sequence contained in Clone ID NO:Z and/or a mature (secreted) polypeptide encoded by the cDNA sequence contained in Clone ID NO:Z.

[171] "Variant" refers to a polynucleotide or polypeptide differing from the polynucleotide or polypeptide of the present invention, but retaining essential properties

thereof. Generally, variants are overall closely similar, and, in many regions, identical to the polynucleotide or polypeptide of the present invention.

[172] Thus, one aspect of the invention provides an isolated nucleic acid molecule comprising, or alternatively consisting of, a polynucleotide having a nucleotide sequence selected from the group consisting of: (a) a nucleotide sequence described in SEQ ID NO:X or contained in the cDNA sequence of Clone ID NO:Z; (b) a nucleotide sequence in SEQ ID NO:X or the cDNA in Clone ID NO:Z which encodes the complete amino acid sequence of SEQ ID NO:Y or the complete amino acid sequence encoded by the cDNA in Clone ID NO:Z; (c) a nucleotide sequence in SEQ ID NO:X or the cDNA in Clone ID NO:Z which encodes a mature polypeptide (i.e., a secreted polypeptide (e.g., as delineated in columns 14 and 15 of Table 1A)); (d) a nucleotide sequence in SEQ ID NO:X or the cDNA sequence of Clone ID NO:Z, which encodes a biologically active fragment of a polypeptide; (e) a nucleotide sequence in SEQ ID NO:X or the cDNA sequence of Clone ID NO:Z, which encodes an antigenic fragment of a polypeptide; (f) a nucleotide sequence encoding a polypeptide comprising the complete amino acid sequence of SEQ ID NO:Y or the complete amino acid sequence encoded by the cDNA in Clone ID NO:Z; (g) a nucleotide sequence encoding a mature polypeptide of the amino acid sequence of SEQ ID NO:Y (i.e., a secreted polypeptide (e.g., as delineated in columns 14 and 15 of Table 1A)) or a mature polypeptide of the amino acid sequence encoded by the cDNA in Clone ID NO:Z; (h) a nucleotide sequence encoding a biologically active fragment of a polypeptide having the complete amino acid sequence of SEQ ID NO:Y or the complete amino acid sequence encoded by the cDNA in Clone ID NO:Z; (i) a nucleotide sequence encoding an antigenic fragment of a polypeptide having the complete amino acid sequence of SEQ ID NO:Y or the complete amino acid sequence encoded by the cDNA in Clone ID NO:Z; and (j) a nucleotide sequence complementary to any of the nucleotide sequences in (a), (b), (c), (d), (e), (f), (g), (h), or (i) above.

The present invention is also directed to nucleic acid molecules which comprise, or alternatively consist of, a nucleotide sequence which is at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100%, identical to, for example, any of the nucleotide sequences in (a), (b), (c), (d), (e), (f), (g), (h), (i), or (j) above, the nucleotide coding sequence in SEQ ID NO:X or the complementary strand thereto, the nucleotide coding sequence of the cDNA contained in Clone ID NO:Z or the complementary strand thereto, a nucleotide sequence encoding the polypeptide of SEQ ID NO:Y, a nucleotide sequence encoding a polypeptide

sequence encoded by the nucleotide sequence in SEQ ID NO:X, a polypeptide sequence encoded by the complement of the polynucleotide sequence in SEQ ID NO:X, a nucleotide sequence encoding the polypeptide encoded by the cDNA contained in Clone ID NO:Z, the nucleotide coding sequence in SEQ ID NO:X as defined in columns 8 and 9 of Table 2 or the complementary strand thereto, a nucleotide sequence encoding the polypeptide encoded by the nucleotide sequence in SEQ ID NO:X as defined in columns 8 and 9 of Table 2 or the complementary strand thereto, the nucleotide coding sequence in SEQ ID NO:B as defined in column 6 of Table 1C or the complementary strand thereto, a nucleotide sequence encoding the polypeptide encoded by the nucleotide sequence in SEQ ID NO:B as defined in column 6 of Table 1C or the complementary strand thereto, the nucleotide sequence in SEQ ID NO:X encoding the polypeptide sequence as defined in column 7 of Table 1B or the complementary strand thereto, nucleotide sequences encoding the polypeptide as defined in column 7 of Table 1B or the complementary strand thereto, and/or polynucleotide fragments of any of these nucleic acid molecules (e.g., those fragments described herein). Polynucleotides which hybridize to the complement of these nucleic acid molecules under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention, as are polypeptides encoded by these polynucleotides and nucleic acids.

In a preferred embodiment, the invention encompasses nucleic acid molecules which comprise, or alternatively, consist of a polynucleotide which hybridizes under stringent hybridization conditions, or alternatively, under lower stringency conditions, to a polynucleotide in (a), (b), (c), (d), (e), (f), (g), (h), or (i), above, as are polypeptides encoded by these polynucleotides. In another preferred embodiment, polynucleotides which hybridize to the complement of these nucleic acid molecules under stringent hybridization conditions, or alternatively, under lower stringency conditions, are also encompassed by the invention, as are polypeptides encoded by these polynucleotides.

In another embodiment, the invention provides a purified protein comprising, or alternatively consisting of, a polypeptide having an amino acid sequence selected from the group consisting of: (a) the complete amino acid sequence of SEQ ID NO:Y or the complete amino acid sequence encoded by the cDNA in Clone ID NO:Z; (b) the amino acid sequence of a mature (secreted) form of a polypeptide having the amino acid sequence of SEQ ID NO:Y (e.g., as delineated in columns 14 and 15 of Table 1A) or a mature form of the amino acid sequence encoded by the cDNA in Clone ID NO:Z mature; (c) the amino

acid sequence of a biologically active fragment of a polypeptide having the complete amino acid sequence of SEQ ID NO:Y or the complete amino acid sequence encoded by the cDNA in Clone ID NO:Z; and (d) the amino acid sequence of an antigenic fragment of a polypeptide having the complete amino acid sequence of SEQ ID NO:Y or the complete amino acid sequence encoded by the cDNA in Clone ID NO:Z.

The present invention is also directed to proteins which comprise, or alternatively [176] consist of, an amino acid sequence which is at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100%, identical to, for example, any of the amino acid sequences in (a), (b), (c), or (d), above, the amino acid sequence shown in SEQ ID NO:Y, the amino acid sequence encoded by the cDNA contained in Clone ID NO:Z, the amino acid sequence of the polypeptide encoded by the nucleotide sequence in SEQ ID NO:X as defined in columns 8 and 9 of Table 2, the amino acid sequence of the polypeptide encoded by the nucleotide sequence in SEQ ID NO:B as defined in column 6 of Table 1C, the amino acid sequence as defined in column 7 of Table 1B, an amino acid sequence encoded by the nucleotide sequence in SEQ ID NO:X, and an amino acid sequence encoded by the complement of the polynucleotide sequence in SEQ ID NO:X. Fragments of these polypeptides are also provided (e.g., those fragments described herein). Further proteins encoded by polynucleotides which hybridize to the complement of the nucleic acid molecules encoding these amino acid sequences under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention, as are the polynucleotides encoding these proteins.

[177] By a nucleic acid having a nucleotide sequence at least, for example, 95% "identical" to a reference nucleotide sequence of the present invention, it is intended that the nucleotide sequence of the nucleic acid is identical to the reference sequence except that the nucleotide sequence may include up to five point mutations per each 100 nucleotides of the reference nucleotide sequence encoding the polypeptide. In other words, to obtain a nucleic acid having a nucleotide sequence at least 95% identical to a reference nucleotide sequence, up to 5% of the nucleotides in the reference sequence may be deleted or substituted with another nucleotide, or a number of nucleotides up to 5% of the total nucleotides in the reference sequence may be inserted into the reference sequence. The query sequence may be an entire sequence referred to in Table 1B or 2 as the ORF (open reading frame), or any fragment specified as described herein.

[178] As a practical matter, whether any particular nucleic acid molecule or

polypeptide is at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to a nucleotide sequence of the present invention can be determined conventionally using known computer programs. A preferred method for determining the best overall match between a query sequence (a sequence of the present invention) and a subject sequence, also referred to as a global sequence alignment, can be determined using the FASTDB computer program based on the algorithm of Brutlag et al. (Comp. App. Biosci. 6:237-245 (1990)). In a sequence alignment the query and subject sequences are both DNA sequences. An RNA sequence can be compared by converting U's to T's. The result of said global sequence alignment is expressed as percent identity. Preferred parameters used in a FASTDB alignment of DNA sequences to calculate percent identity are: Matrix=Unitary, k-tuple=4, Mismatch Penalty=1, Joining Penalty=30, Randomization Group Length=0, Cutoff Score=1, Gap Penalty=5, Gap Size Penalty 0.05, Window Size=500 or the length of the subject nucleotide sequence, whichever is shorter.

[179] If the subject sequence is shorter than the query sequence because of 5' or 3' deletions, not because of internal deletions, a manual correction must be made to the results. This is because the FASTDB program does not account for 5' and 3' truncations of the subject sequence when calculating percent identity. For subject sequences truncated at the 5' or 3' ends, relative to the query sequence, the percent identity is corrected by calculating the number of bases of the query sequence that are 5' and 3' of the subject sequence, which are not matched/aligned, as a percent of the total bases of the query sequence. Whether a nucleotide is matched/aligned is determined by results of the FASTDB sequence alignment. This percentage is then subtracted from the percent identity, calculated by the above FASTDB program using the specified parameters, to arrive at a final percent identity score. This corrected score is what is used for the purposes of the present invention. Only bases outside the 5' and 3' bases of the subject sequence, as displayed by the FASTDB alignment, which are not matched/aligned with the query sequence, are calculated for the purposes of manually adjusting the percent identity score.

[180] For example, a 90 base subject sequence is aligned to a 100 base query sequence to determine percent identity. The deletions occur at the 5' end of the subject sequence and therefore, the FASTDB alignment does not show a matched/alignment of the first 10 bases at 5' end. The 10 unpaired bases represent 10% of the sequence (number of bases at the 5' and 3' ends not matched/total number of bases in the query sequence) so 10% is subtracted from the percent identity score calculated by the FASTDB program. If the remaining 90

bases were perfectly matched the final percent identity would be 90%. In another example, a 90 base subject sequence is compared with a 100 base query sequence. This time the deletions are internal deletions so that there are no bases on the 5' or 3' of the subject sequence which are not matched/aligned with the query. In this case the percent identity calculated by FASTDB is not manually corrected. Once again, only bases 5' and 3' of the subject sequence which are not matched/aligned with the query sequence are manually corrected for. No other manual corrections are to be made for the purposes of the present invention.

[181] By a polypeptide having an amino acid sequence at least, for example, 95% "identical" to a query amino acid sequence of the present invention, it is intended that the amino acid sequence of the subject polypeptide is identical to the query sequence except that the subject polypeptide sequence may include up to five amino acid alterations per each 100 amino acids of the query amino acid sequence. In other words, to obtain a polypeptide having an amino acid sequence at least 95% identical to a query amino acid sequence, up to 5% of the amino acid residues in the subject sequence may be inserted, deleted, (indels) or substituted with another amino acid. These alterations of the reference sequence may occur at the amino or carboxy terminal positions of the reference amino acid sequence or anywhere between those terminal positions, interspersed either individually among residues in the reference sequence or in one or more contiguous groups within the reference sequence.

[182] As a practical matter, whether any particular polypeptide is at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to, for instance, the amino acid sequence of a polypeptide referred to in Table 1A (e.g., the amino acid sequence delineated in columns 14 and 15) or a fragment thereof, Table 1B (e.g., the amino acid sequence identified in column 6) or a fragment thereof, Table 2 (e.g., the amino acid sequence of the polypeptide encoded by the polynucleotide sequence defined in columns 8 and 9 of Table 2) or a fragment thereof, the amino acid sequence of the polypeptide encoded by the polynucleotide sequence in SEQ ID NO:B as defined in column 6 of Table 1C or a fragment thereof, the amino acid sequence of the polypeptide encoded by the nucleotide sequence in SEQ ID NO:X or a fragment thereof, or the amino acid sequence of the polypeptide encoded by cDNA contained in Clone ID NO:Z, or a fragment thereof, the amino acid sequence of a mature (secreted) polypeptide encoded by cDNA contained in Clone ID NO:Z, or a fragment thereof, can be determined conventionally using known computer programs. A

preferred method for determining the best overall match between a query sequence (a sequence of the present invention) and a subject sequence, also referred to as a global sequence alignment, can be determined using the FASTDB computer program based on the algorithm of Brutlag et al. (Comp. App. Biosci.6:237-245 (1990)). In a sequence alignment the query and subject sequences are either both nucleotide sequences or both amino acid sequences. The result of said global sequence alignment is expressed as percent identity. Preferred parameters used in a FASTDB amino acid alignment are: Matrix=PAM 0, k-tuple=2, Mismatch Penalty=1, Joining Penalty=20, Randomization Group Length=0, Cutoff Score=1, Window Size=sequence length, Gap Penalty=5, Gap Size Penalty=0.05, Window Size=500 or the length of the subject amino acid sequence, whichever is shorter.

[183] If the subject sequence is shorter than the query sequence due to N- or C-terminal deletions, not because of internal deletions, a manual correction must be made to the results. This is because the FASTDB program does not account for N- and C-terminal truncations of the subject sequence when calculating global percent identity. For subject sequences truncated at the N- and C-termini, relative to the query sequence, the percent identity is corrected by calculating the number of residues of the query sequence that are N- and Cterminal of the subject sequence, which are not matched/aligned with a corresponding subject residue, as a percent of the total bases of the query sequence. Whether a residue is matched/aligned is determined by results of the FASTDB sequence alignment. This percentage is then subtracted from the percent identity, calculated by the above FASTDB program using the specified parameters, to arrive at a final percent identity score. This final percent identity score is what is used for the purposes of the present invention. Only residues to the N- and C-termini of the subject sequence, which are not matched/aligned with the query sequence, are considered for the purposes of manually adjusting the percent identity score. That is, only query residue positions outside the farthest N- and C- terminal residues of the subject sequence.

[184] For example, a 90 amino acid residue subject sequence is aligned with a 100 residue query sequence to determine percent identity. The deletion occurs at the N-terminus of the subject sequence and therefore, the FASTDB alignment does not show a matching/alignment of the first 10 residues at the N-terminus. The 10 unpaired residues represent 10% of the sequence (number of residues at the N- and C- termini not matched/total number of residues in the query sequence) so 10% is subtracted from the percent identity score calculated by the FASTDB program. If the remaining 90 residues

were perfectly matched the final percent identity would be 90%. In another example, a 90 residue subject sequence is compared with a 100 residue query sequence. This time the deletions are internal deletions so there are no residues at the N- or C-termini of the subject sequence which are not matched/aligned with the query. In this case the percent identity calculated by FASTDB is not manually corrected. Once again, only residue positions outside the N- and C-terminal ends of the subject sequence, as displayed in the FASTDB alignment, which are not matched/aligned with the query sequence are manually corrected for. No other manual corrections are to made for the purposes of the present invention.

[185] The polynucleotide variants of the invention may contain alterations in the coding regions, non-coding regions, or both. Especially preferred are polynucleotide variants containing alterations which produce silent substitutions, additions, or deletions, but do not alter the properties or activities of the encoded polypeptide. Nucleotide variants produced by silent substitutions due to the degeneracy of the genetic code are preferred. Moreover, polypeptide variants in which less than 50, less than 40, less than 30, less than 20, less than 10, or 5-50, 5-25, 5-10, 1-5, or 1-2 amino acids are substituted, deleted, or added in any combination are also preferred. Polynucleotide variants can be produced for a variety of reasons, e.g., to optimize codon expression for a particular host (change codons in the human mRNA to those preferred by a bacterial host such as E. coli).

[186] Naturally occurring variants are called "allelic variants," and refer to one of several alternate forms of a gene occupying a given locus on a chromosome of an organism. (Genes II, Lewin, B., ed., John Wiley & Sons, New York (1985)). These allelic variants can vary at either the polynucleotide and/or polypeptide level and are included in the present invention. Alternatively, non-naturally occurring variants may be produced by mutagenesis techniques or by direct synthesis.

Using known methods of protein engineering and recombinant DNA technology, variants may be generated to improve or alter the characteristics of the polypeptides of the present invention. For instance, one or more amino acids can be deleted from the N-terminus or C-terminus of the polypeptide of the present invention without substantial loss of biological function. As an example, Ron et al. (J. Biol. Chem. 268: 2984-2988 (1993)) reported variant KGF proteins having heparin binding activity even after deleting 3, 8, or 27 amino-terminal amino acid residues. Similarly, Interferon gamma exhibited up to ten times higher activity after deleting 8-10 amino acid residues from the carboxy terminus of this protein. (Dobeli et al., J. Biotechnology 7:199-216 (1988).)

[188] Moreover, ample evidence demonstrates that variants often retain a biological activity similar to that of the naturally occurring protein. For example, Gayle and coworkers (J. Biol. Chem. 268:22105-22111 (1993)) conducted extensive mutational analysis of human cytokine IL-1a. They used random mutagenesis to generate over 3,500 individual IL-1a mutants that averaged 2.5 amino acid changes per variant over the entire length of the molecule. Multiple mutations were examined at every possible amino acid position. The investigators found that "[m]ost of the molecule could be altered with little effect on either [binding or biological activity]." In fact, only 23 unique amino acid sequences, out of more than 3,500 nucleotide sequences examined, produced a protein that significantly differed in activity from wild-type.

[189] Furthermore, even if deleting one or more amino acids from the N-terminus or C-terminus of a polypeptide results in modification or loss of one or more biological functions, other biological activities may still be retained. For example, the ability of a deletion variant to induce and/or to bind antibodies which recognize the secreted form will. likely be retained when less than the majority of the residues of the secreted form are removed from the N-terminus or C-terminus. Whether a particular polypeptide lacking N-or C-terminal residues of a protein retains such immunogenic activities can readily be determined by routine methods described herein and otherwise known in the art.

[190] Thus, the invention further includes polypeptide variants which show a functional activity (e.g., biological activity) of the polypeptides of the invention. Such variants include deletions, insertions, inversions, repeats, and substitutions selected according to general rules known in the art so as have little effect on activity.

[191] The present application is directed to nucleic acid molecules at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleic acid sequences disclosed herein, (e.g., encoding a polypeptide having the amino acid sequence of an N and/or C terminal deletion), irrespective of whether they encode a polypeptide having functional activity. This is because even where a particular nucleic acid molecule does not encode a polypeptide having functional activity, one of skill in the art would still know how to use the nucleic acid molecule, for instance, as a hybridization probe or a polymerase chain reaction (PCR) primer. Uses of the nucleic acid molecules of the present invention that do not encode a polypeptide having functional activity include, inter alia, (1) isolating a gene or allelic or splice variants thereof in a cDNA library; (2) in situ hybridization (e.g., "FISH") to metaphase chromosomal spreads to provide precise chromosomal location of the

gene, as described in Verma et al., Human Chromosomes: A Manual of Basic Techniques, Pergamon Press, New York (1988); (3) Northern Blot analysis for detecting mRNA expression in specific tissues (e.g., normal or diseased tissues); and (4) *in situ* hybridization (e.g., histochemistry) for detecting mRNA expression in specific tissues (e.g., normal or diseased tissues).

Preferred, however, are nucleic acid molecules having sequences at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleic acid sequences disclosed herein, which do, in fact, encode a polypeptide having functional activity. By a polypeptide having "functional activity" is meant, a polypeptide capable of displaying one or more known functional activities associated with a full-length (complete) protein and/or a mature (secreted) protein of the invention. Such functional activities include, but are not limited to, biological activity, antigenicity [ability to bind (or compete with a polypeptide of the invention for binding) to an anti-polypeptide of the invention antibody], immunogenicity (ability to generate antibody which binds to a specific polypeptide of the invention), ability to form multimers with polypeptides of the invention, and ability to bind to a receptor or ligand for a polypeptide of the invention.

[193] The functional activity of the polypeptides, and fragments, variants and derivatives of the invention, can be assayed by various methods.

[194] For example, in one embodiment where one is assaying for the ability to bind or compete with a full-length polypeptide of the present invention for binding to an antipolypetide antibody, various immunoassays known in the art can be used, including but not limited to, competitive and non-competitive assay systems using techniques such as radioimmunoassays, ELISA (enzyme linked immunosorbent assay), "sandwich" immunoassays, immunoradiometric assays, gel diffusion precipitation reactions, immunodiffusion assays, in situ immunoassays (using colloidal gold, enzyme or radioisotope labels, for example), western blots, precipitation reactions, agglutination assays (e.g., gel agglutination assays, hemagglutination assays), complement fixation assays, immunofluorescence assays, protein A assays, and immunoelectrophoresis assays, etc. In one embodiment, antibody binding is detected by detecting a label on the primary antibody. In another embodiment, the primary antibody is detected by detecting binding of a secondary antibody or reagent to the primary antibody. In a further embodiment, the secondary antibody is labeled. Many means are known in the art for detecting binding in an immunoassay and are within the scope of the present invention.

[195] In another embodiment, where a ligand is identified, or the ability of a polypeptide fragment, variant or derivative of the invention to multimerize is being evaluated, binding can be assayed, e.g., by means well-known in the art, such as, for example, reducing and non-reducing gel chromatography, protein affinity chromatography, and affinity blotting. See generally, Phizicky et al., Microbiol. Rev. 59:94-123 (1995). In another embodiment, the ability of physiological correlates of a polypeptide of the present invention to bind to a substrate(s) of the polypeptide of the invention can be routinely assayed using techniques known in the art.

[196] In addition, assays described herein (see Examples) and otherwise known in the art may routinely be applied to measure the ability of polypeptides of the present invention and fragments, variants and derivatives thereof to elicit polypeptide related biological activity (either *in vitro* or *in vivo*). Other methods will be known to the skilled artisan and are within the scope of the invention.

[197] Of course, due to the degeneracy of the genetic code, one of ordinary skill in the art will immediately recognize that a large number of the nucleic acid molecules having a sequence at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to, for example, the nucleic acid sequence of the cDNA contained in Clone ID NO:Z, the nucleic acid sequence referred to in Table 1B (SEQ ID NO:X),), the nucleic acid sequence disclosed in Table 1A (e.g., the nucleic acid sequence delineated in columns 7 and 8), the nucleic acid sequence disclosed in Table 2 (e.g., the nucleic acid sequence delineated in columns 8 and 9) or fragments thereof, will encode polypeptides "having functional activity." In fact, since degenerate variants of any of these nucleotide sequences all encode the same polypeptide, in many instances, this will be clear to the skilled artisan even without performing the above described comparison assay. It will be further recognized in the art that, for such nucleic acid molecules that are not degenerate variants, a reasonable number will also encode a polypeptide having functional activity. This is because the skilled artisan is fully aware of amino acid substitutions that are either less likely or not likely to significantly effect protein function (e.g., replacing one aliphatic amino acid with a second aliphatic amino acid), as further described below.

[198] For example, guidance concerning how to make phenotypically silent amino acid substitutions is provided in Bowie et al., "Deciphering the Message in Protein Sequences: Tolerance to Amino Acid Substitutions," Science 247:1306-1310 (1990), wherein the

authors indicate that there are two main strategies for studying the tolerance of an amino acid sequence to change.

[199] The first strategy exploits the tolerance of amino acid substitutions by natural selection during the process of evolution. By comparing amino acid sequences in different species, conserved amino acids can be identified. These conserved amino acids are likely important for protein function. In contrast, the amino acid positions where substitutions have been tolerated by natural selection indicates that these positions are not critical for protein function. Thus, positions tolerating amino acid substitution could be modified while still maintaining biological activity of the protein.

[200] The second strategy uses genetic engineering to introduce amino acid changes at specific positions of a cloned gene to identify regions critical for protein function. For example, site directed mutagenesis or alanine-scanning mutagenesis (introduction of single alanine mutations at every residue in the molecule) can be used. See Cunningham and Wells, Science 244:1081-1085 (1989). The resulting mutant molecules can then be tested for biological activity.

[201] As the authors state, these two strategies have revealed that proteins are surprisingly tolerant of amino acid substitutions. The authors further indicate which amino acid changes are likely to be permissive at certain amino acid positions in the protein. For example, most buried (within the tertiary structure of the protein) amino acid residues require nonpolar side chains, whereas few features of surface side chains are generally conserved. Moreover, tolerated conservative amino acid substitutions involve replacement of the aliphatic or hydrophobic amino acids Ala, Val, Leu and Ile; replacement of the hydroxyl residues Ser and Thr; replacement of the acidic residues Asp and Glu; replacement of the amide residues Asn and Gln, replacement of the basic residues Lys, Arg, and His; replacement of the aromatic residues Phe, Tyr, and Trp, and replacement of the small-sized amino acids Ala, Ser, Thr, Met, and Gly.

[202] Besides conservative amino acid substitution, variants of the present invention include (i) substitutions with one or more of the non-conserved amino acid residues, where the substituted amino acid residues may or may not be one encoded by the genetic code, or (ii) substitutions with one or more of the amino acid residues having a substituent group, or (iii) fusion of the mature polypeptide with another compound, such as a compound to increase the stability and/or solubility of the polypeptide (for example, polyethylene glycol), (iv) fusion of the polypeptide with additional amino acids, such as, for example, an

IgG Fc fusion region peptide, serum albumin (preferably human serum albumin) or a fragment thereof, or leader or secretory sequence, or a sequence facilitating purification, or (v) fusion of the polypeptide with another compound, such as albumin (including but not limited to recombinant albumin (see, e.g., U.S. Patent No. 5,876,969, issued March 2, 1999, EP Patent 0 413 622, and U.S. Patent No. 5,766,883, issued June 16, 1998, herein incorporated by reference in their entirety)). Such variant polypeptides are deemed to be within the scope of those skilled in the art from the teachings herein.

[203] For example, polypeptide variants containing amino acid substitutions of charged amino acids with other charged or neutral amino acids may produce proteins with improved characteristics, such as less aggregation. Aggregation of pharmaceutical formulations both reduces activity and increases clearance due to the aggregate's immunogenic activity. See Pinckard et al., Clin. Exp. Immunol. 2:331-340 (1967); Robbins et al., Diabetes 36: 838-845 (1987); Cleland et al., Crit. Rev. Therapeutic Drug Carrier Systems 10:307-377 (1993).

A further embodiment of the invention relates to polypeptides which comprise [204] the amino acid sequence of a polypeptide having an amino acid sequence which contains at least one amino acid substitution, but not more than 50 amino acid substitutions, even more preferably, not more than 40 amino acid substitutions, still more preferably, not more than 30 amino acid substitutions, and still even more preferably, not more than 20 amino acid substitutions from a polypeptide sequence disclosed herein. Of course it is highly preferable for a polypeptide to have an amino acid sequence which, for example, comprises the amino acid sequence of a polypeptide of SEQ ID NO:Y, the amino acid sequence of the mature (e.g., secreted) polypeptide of SEQ ID NO:Y, an amino acid sequence encoded by SEQ ID NO:X, an amino acid sequence encoded by the portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2, an amino acid sequence encoded by the complement of SEQ ID NO:X, an amino acid sequence encoded by cDNA contained in Clone ID NO:Z, and/or the amino acid sequence of a mature (secreted) polypeptide encoded by cDNA contained in Clone ID NO:Z, or a fragment thereof, which contains, in order of everincreasing preference, at least one, but not more than 10, 9, 8, 7, 6, 5, 4, 3, 2 or 1 amino acid substitutions.

[205] In specific embodiments, the polypeptides of the invention comprise, or alternatively, consist of, fragments or variants of a reference amino acid sequence selected from: (a) the amino acid sequence of SEQ ID NO:Y or fragments thereof (e.g., the mature formand/or other fragments described herein); (b) the amino acid sequence encoded by SEQ

ID NO:X or fragments thereof; (c) the amino acid sequence encoded by the complement of SEQ ID NO:X or fragments thereof; (d) the amino acid sequence encoded by the portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2 or fragments thereof; and (e) the amino acid sequence encoded by cDNA contained in Clone ID NO:Z or fragments thereof; wherein the fragments or variants have 1-5, 5-10, 5-25, 5-50, 10-50 or 50-150, amino acid residue additions, substitutions, and/or deletions when compared to the reference amino acid sequence. In preferred embodiments, the amino acid substitutions are conservative. Polynucleotides encoding these polypeptides are also encompassed by the invention.

Polynucleotide and Polypeptide Fragments

[206] The present invention is also directed to polynucleotide fragments of the polynucleotides (nucleic acids) of the invention. In the present invention, a "polynucleotide fragment" refers to a polynucleotide having a nucleic acid sequence which, for example: is a portion of the cDNA contained in Clone ID NO:Z or the complementary strand thereto; is a portion of the polynucleotide sequence encoding the polypeptide encoded by the cDNA contained in Clone ID NO:Z or the complementary strand thereto; is a portion of the polynucleotide sequence encoding the mature (secreted) polypeptide encoded by the cDNA contained in Clone ID NO:Z or the complementary strand thereto; is a portion of a polynucleotide sequence encoding the mature amino acid sequence as defined in columns 14 and 15 of Table 1A or the complementary strand thereto; is a portion of a polynucleotide sequence encoding the amino acid sequence encoded by the region of SEO ID NO:X as defined in columns 8 and 9 of Table 2 or the complementary strand thereto; is a portion of the polynucleotide sequence of SEQ ID NO:X as defined in columns 8 and 9 of Table 2 or the complementary strand thereto; is a portion of the polynucleotide sequence in SEQ ID NO:X or the complementary strand thereto; is a polynucleotide sequence encoding a portion of the polypeptide of SEQ ID NO:Y; is a polynucleotide sequence encoding a portion of a polypeptide encoded by SEQ ID NO:X; is a polynucleotide sequence encoding a portion of a polypeptide encoded by the complement of the polynucleotide sequence in SEQ ID NO:X; is a portion of a polynucleotide sequence encoding the amino acid sequence encoded by the region of SEQ ID NO:B as defined in column 6 of Table 1C or the complementary strand thereto; or is a portion of the polynucleotide sequence of SEQ ID NO:B as defined in column 6 of Table 1C or the complementary strand thereto.

The polynucleotide fragments of the invention are preferably at least about 15 nt, and more preferably at least about 20 nt, still more preferably at least about 30 nt, and even more preferably, at least about 40 nt, at least about 50 nt, at least about 75 nt, or at least about 150 nt in length. A fragment "at least 20 nt in length," for example, is intended to include 20 or more contiguous bases from the cDNA sequence contained in Clone ID NO:Z, or the nucleotide sequence shown in SEQ ID NO:X or the complementary stand thereto. In this context "about" includes the particularly recited value or a value larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. These nucleotide fragments have uses that include, but are not limited to, as diagnostic probes and primers as discussed herein. Of course, larger fragments (e.g., at least 160, 170, 180, 190, 200, 250, 500, 600, 1000, or 2000 nucleotides in length) are also encompassed by the invention.

[208] Moreover, representative examples of polynucleotide fragments of the invention comprise, or alternatively consist of, a sequence from about nucleotide number 1-50, 51-100, 101-150, 151-200, 201-250, 251-300, 301-350, 351-400, 401-450, 451-500, 501-550, 551-600, 601-650, 651-700, 701-750, 751-800, 801-850, 851-900, 901-950, 951-1000, 1001-1050, 1051-1100, 1101-1150, 1151-1200, 1201-1250, 1251-1300, 1301-1350, 1351-1400, 1401-1450, 1451-1500, 1501-1550, 1551-1600, 1601-1650, 1651-1700, 1701-1750, 1751-1800, 1801-1850, 1851-1900, 1901-1950, 1951-2000, 2001-2050, 2051-2100, 2101-2150, 2151-2200, 2201-2250, 2251-2300, 2301-2350, 2351-2400, 2401-2450, 2451-2500, 2501-2550, 2551-2600, 2601-2650, 2651-2700, 2701-2750, 2751-2800, 2801-2850, 2851-2900, 2901-2950, 2951-3000, 3001-3050, 3051-3100, 3101-3150, 3151-3200, 3201-3250, 3251-3300, 3301-3350, 3351-3400, 3401-3450, 3451-3500, 3501-3550, 3551-3600, 3601-3650, 3651-3700, 3701-3750, 3751-3800, 3801-3850, 3851-3900, 3901-3950, 3951-4000, 4001-4050, 4051-4100, 4101-4150, 4151-4200, 4201-4250, 4251-4300, 4301-4350, 4351-4400, 4401-4450, 4451-4500, 4501-4550, 4551-4600, 4601-4650, 4651-4700, 4701-4750, 4751-4800, 4801-4850, 4851-4900, 4901-4950, 4951-5000, 5001-5050, 5051-5100, 5101-5150, 5151-5200, 5201-5250, 5251-5300, 5301-5350, 5351-5400, 5401-5450, 5451-5500, 5501-5550, 5551-5600, 5601-5650, 5651-5700, 5701-5750, 5751-5800, 5801-5850, 5851-5900, 5901-5950, 5951-6000, 6001-6050, 6051-6100, 6101-6150, 6151-6200, 6201-6250, 6251-6300, 6301-6350, 6351-6400, 6401-6450, 6451-6500, 6501-6550, 6551-6600, 6601-6650, 6651-6700, 6701-6750, 6751-6800, 6801-6850, 6851-6900, 6901-6950, 6951-7000, 7001-7050, 7051-7100, 7101-7150, 7151-7200, 7201-7250, 7251-7300 or 7301 to the end

of SEQ ID NO:X, or the complementary strand thereto. In this context "about" includes the particularly recited range or a range larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. Preferably, these fragments encode a polypeptide which has a functional activity (e.g., biological activity). More preferably, these polynucleotides can be used as probes or primers as discussed herein. Polynucleotides which hybridize to one or more of these polynucleotides under stringent hybridization conditions or alternatively, under lower stringency conditions are also encompassed by the invention, as are polypeptides encoded by these polynucleotides.

[209] Further representative examples of polynucleotide fragments of the invention comprise, or alternatively consist of, a sequence from about nucleotide number 1-50, 51-100, 101-150, 151-200, 201-250, 251-300, 301-350, 351-400, 401-450, 451-500, 501-550, 551-600, 601-650, 651-700, 701-750, 751-800, 801-850, 851-900, 901-950, 951-1000, 1001-1050, 1051-1100, 1101-1150, 1151-1200, 1201-1250, 1251-1300, 1301-1350, 1351-1400, 1401-1450, 1451-1500, 1501-1550, 1551-1600, 1601-1650, 1651-1700, 1701-1750, 1751-1800, 1801-1850, 1851-1900, 1901-1950, 1951-2000, 2001-2050, 2051-2100, 2101-2150, 2151-2200, 2201-2250, 2251-2300, 2301-2350, 2351-2400, 2401-2450, 2451-2500, 2501-2550, 2551-2600, 2601-2650, 2651-2700, 2701-2750, 2751-2800, 2801-2850, 2851-2900, 2901-2950, 2951-3000, 3001-3050, 3051-3100, 3101-3150, 3151-3200, 3201-3250, 3251-3300, 3301-3350, 3351-3400, 3401-3450, 3451-3500, 3501-3550, 3551-3600, 3601-3650, 3651-3700, 3701-3750, 3751-3800, 3801-3850, 3851-3900, 3901-3950, 3951-4000, 4001-4050, 4051-4100, 4101-4150, 4151-4200, 4201-4250, 4251-4300, 4301-4350, 4351-4400, 4401-4450, 4451-4500, 4501-4550, 4551-4600, 4601-4650, 4651-4700, 4701-4750, 4751-4800, 4801-4850, 4851-4900, 4901-4950, 4951-5000, 5001-5050, 5051-5100, 5101-5150, 5151-5200, 5201-5250, 5251-5300, 5301-5350, 5351-5400, 5401-5450, 5451-5500, 5501-5550, 5551-5600, 5601-5650, 5651-5700, 5701-5750, 5751-5800, 5801-5850, 5851-5900, 5901-5950, 5951-6000, 6001-6050, 6051-6100, 6101-6150, 6151-6200, 6201-6250, 6251-6300, 6301-6350, 6351-6400, 6401-6450, 6451-6500, 6501-6550, 6551-6600, 6601-6650, 6651-6700, 6701-6750, 6751-6800, 6801-6850, 6851-6900, 6901-6950, 6951-7000, 7001-7050, 7051-7100, 7101-7150, 7151-7200, 7201-7250, 7251-7300 or 7301 to the end of the cDNA sequence contained in Clone ID NO:Z, or the complementary strand thereto. In this context "about" includes the particularly recited range or a range larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. Preferably, these fragments encode a polypeptide which has a functional activity (e.g., biological activity).

More preferably, these polynucleotides can be used as probes or primers as discussed herein. Polynucleotides which hybridize to one or more of these polynucleotides under stringent hybridization conditions or alternatively, under lower stringency conditions are also encompassed by the invention, as are polypeptides encoded by these polynucleotides.

[210] Moreover, representative examples of polynucleotide fragments of the invention comprise, or alternatively consist of, a nucleic acid sequence comprising one, two, three, four, five, six, seven, eight, nine, ten, or more of the above described polynucleotide fragments of the invention in combination with a polynucleotide sequence delineated in Table 1C column 6. Additional, representative examples of polynucleotide fragments of the invention comprise, or alternatively consist of, a nucleic acid sequence comprising one, two, three, four, five, six, seven, eight, nine, ten, or more of the above described polynucleotide fragments of the invention in combination with a polynucleotide sequence that is the complementary strand of a sequence delineated in column 6 of Table 1C. further embodiments, the above-described polynucleotide fragments of the invention comprise, or alternatively consist of, sequences delineated in Table 1C, column 6, and have a nucleic acid sequence which is different from that of the BAC fragment having the sequence disclosed in SEQ ID NO:B (see Table 1C, column 5). In additional embodiments, the above-described polynucleotide fragments of the invention comprise, or alternatively consist of, sequences delineated in Table 1C, column 6, and have a nucleic acid sequence which is different from that published for the BAC clone identified as BAC ID NO:A (see Table 1C, column 4). In additional embodiments, the above-described polynucleotides of the invention comprise, or alternatively consist of, sequences delineated Table 1C, column 6, and have a nucleic acid sequence which is different from that contained in the BAC clone identified as BAC ID NO:A (see Table 1C, column 4). Polypeptides encoded by these polynucleotides, other polynucleotides that encode these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides and polypeptides are also encompassed by the invention.

[211] In additional specific embodiments, polynucleotides of the invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, eight, nine, ten, or more fragments of the sequences delineated in column 6 of Table 1C, and the polynucleotide sequence of SEQ ID NO:X (e.g., as defined in Table 1C, column 2) or fragments or variants thereof. Polypeptides encoded by these polynucleotides, other polynucleotides that encode

these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention.

In additional specific embodiments, polynucleotides of the invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, eight, nine, ten, or more fragments of the sequences delineated in column 6 of Table 1C which correspond to the same Clone ID NO:Z (see Table 1C, column 1), and the polynucleotide sequence of SEQ ID NO:X (e.g., as defined in Table 1A, 1B, or 1C) or fragments or variants thereof. Polypeptides encoded by these polynucleotides, other polynucleotides that encode these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention.

[213] In further specific embodiments, polynucleotides of the invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, eight, nine, ten, or more fragments of the sequences delineated in the same row of column 6 of Table 1C, and the polynucleotide sequence of SEQ ID NO:X (e.g., as defined in Table 1A, 1B, or 1C) or fragments or variants thereof. Polypeptides encoded by these polynucleotides, other polynucleotides that encode these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention.

In additional specific embodiments, polynucleotides of the invention comprise, or alternatively consist of a polynucleotide sequence in which the 3' 10 polynucleotides of one of the sequences delineated in column 6 of Table 1C and the 5' 10 polynucleotides of the sequence of SEQ ID NO:X are directly contiguous. Nucleic acids which hybridize to the complement of these 20 contiguous polynucleotides under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention. Polypeptides encoded by these polynucleotides and/or nucleic acids, other polynucleotides and/or nucleic acids that encode these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides, nucleic acids, and polypeptides are also encompassed by the invention.

[215] In additional specific embodiments, polynucleotides of the invention comprise, or alternatively consist of a polynucleotide sequence in which the 3' 10 polynucleotides of one of the sequences delineated in column 6 of Table 1C and the 5' 10 polynucleotides of a fragment or variant of the sequence of SEQ ID NO:X (e.g., as described herein) are directly contiguous Nucleic acids which hybridize to the complement of these 20 contiguous

polynucleotides under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention. Polypeptides encoded by these polynucleotides and/or nucleic acids, other polynucleotides and/or nucleic acids encoding these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides, nucleic acids, and polypeptides are also encompassed by the invention.

In further specific embodiments, polynucleotides of the invention comprise, or alternatively consist of a polynucleotide sequence in which the 3' 10 polynucleotides of a fragment or variant of the sequence of SEQ ID NO:X and the 5' 10 polynucleotides of the sequence of one of the sequences delineated in column 6 of Table 1C are directly contiguous. Nucleic acids which hybridize to the complement of these 20 contiguous polynucleotides under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention. Polypeptides encoded by these polynucleotides and/or nucleic acids, other polynucleotides and/or nucleic acids encoding these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides, nucleic acids, and polypeptides are also encompassed by the invention.

[217] In specific embodiments, polynucleotides of the invention comprise, or alternatively consist of a polynucleotide sequence in which the 3' 10 polynucleotides of one of the sequences delineated in column 6 of Table 1C and the 5' 10 polynucleotides of another sequence in column 6 are directly contiguous. In preferred embodiments, the 3' 10 polynucleotides of one of the sequences delineated in column 6 of Table 1C is directly contiguous with the 5' 10 polynucleotides of the next sequential exon delineated in Table 1C, column 6. Nucleic acids which hybridize to the complement of these 20 contiguous polynucleotides under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention. Polypeptides encoded by these polynucleotides and/or nucleic acids, other polynucleotides and/or nucleic acids encoding these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides, nucleic acids, and polypeptides are also encompassed by the invention.

[218] In the present invention, a "polypeptide fragment" refers to an amino acid sequence which is a portion of the amino acid sequence contained in SEQ ID NO:Y, is a portion of the mature form of SEQ ID NO:Y as defined in columns 14 and 15 of Table 1A,

a portion of an amino acid sequence encoded by the portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2, is a portion of an amino acid sequence encoded by the polynucleotide sequence of SEQ ID NO:X, is a portion of an amino acid sequence encoded by the complement of the polynucleotide sequence in SEQ ID NO:X, is a portion of the amino acid sequence of a mature (secreted) polypeptide encoded by the cDNA contained in Clone ID NO:Z, and/or is a portion of an amino acid sequence encoded by the cDNA contained in Clone ID NO:Z. Protein (polypeptide) fragments may be "free-standing," or comprised within a larger polypeptide of which the fragment forms a part or region, most preferably as a single continuous region. Representative examples of polypeptide fragments of the invention, include, for example, fragments comprising, or alternatively consisting of, from about amino acid number 1-20, 21-40, 41-60, 61-80, 81-100, 101-120, 121-140, 141-160, 161-180, 181-200, 201-220, 221-240, 241-260, 261-280, 281-300, 301-320, 321-340, 341-360, 361-380, 381-400, 401-420, 421-440, 441-460, 461-480, 481-500, 501-520, 521-540, 541-560, 561-580, 581-600, 601-620, 621-640, 641-660, 661-680, 681-700, 701-720, 721-740, 741-760, 761-780, 781-800, 801-820, 821-840, 841-860, 861-880, 881-900, 901-920, 921-940, 941-960, 961-980, 981-1000, 1001-1020, 1021-1040, 1041-1060, 1061-1080, 1081-1100, 1101-1120, 1121-1140, 1141-1160, 1161-1180, 1181-1200, 1201-1220, 1221-1240, 1241-1260, 1261-1280, 1281-1300, 1301-1320, 1321-1340, 1341-1360, 1361-1380, 1381-1400, 1401-1420, 1421-1440, or 1441 to the end of the coding region of cDNA and SEQ ID NO: Y. In a preferred embodiment, polypeptide fragments of the invention include, for example, fragments comprising, or alternatively consisting of, from about amino acid number 1-20, 21-40, 41-60, 61-80, 81-100, 101-120, 121-140, 141-160, 161-180, 181-200, 201-220, 221-240, 241-260, 261-280, 281-300, 301-320, 321-340, 341-360, 361-380, 381-400, 401-420, 421-440, 441-460, 461-480, 481-500, 501-520, 521-540, 541-560, 561-580, 581-600, 601-620, 621-640, 641-660, 661-680, 681-700, 701-720, 721-740, 741-760, 761-780, 781-800, 801-820, 821-840, 841-860, 861-880, 881-900, 901-920, 921-940, 941-960, 961-980, 981-1000, 1001-1020, 1021-1040, 1041-1060, 1061-1080. 1081-1100, 1101-1120, 1121-1140, 1141-1160, 1161-1180, 1181-1200, 1201-1220, 1221-1240, 1241-1260, 1261-1280, 1281-1300, 1301-1320, 1321-1340, 1341-1360, 1361-1380, 1381-1400, 1401-1420, 1421-1440, or 1441 to the end of the coding region of SEQ ID NO:Y. Moreover, polypeptide fragments of the invention may be at least about 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 100, 110, 120, 130, 140, or 150 amino acids in length. In this context "about" includes the particularly recited ranges or values, or

ranges or values larger or smaller by several (5, 4, 3, 2, or 1) amino acids, at either extreme or at both extremes. Polynucleotides encoding these polypeptide fragments are also encompassed by the invention.

Even if deletion of one or more amino acids from the N-terminus of a protein results in modification of loss of one or more biological functions of the protein, other functional activities (e.g., biological activities, ability to multimerize, ability to bind a ligand) may still be retained. For example, the ability of shortened muteins to induce and/or bind to antibodies which recognize the complete or mature forms of the polypeptides generally will be retained when less than the majority of the residues of the complete or mature polypeptide are removed from the N-terminus. Whether a particular polypeptide lacking N-terminal residues of a complete polypeptide retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art. It is not unlikely that a mutein with a large number of deleted N-terminal amino acid residues may retain some biological or immunogenic activities. In fact, peptides composed of as few as six amino acid residues may often evoke an immune response.

[220] Accordingly, polypeptide fragments include the secreted protein as well as the mature form. Further preferred polypeptide fragments include the secreted protein or the mature form having a continuous series of deleted residues from the amino or the carboxy terminus, or both. For example, any number of amino acids, ranging from 1-60, can be deleted from the amino terminus of either the secreted polypeptide or the mature form. Similarly, any number of amino acids, ranging from 1-30, can be deleted from the carboxy terminus of the secreted protein or mature form. Furthermore, any combination of the above amino and carboxy terminus deletions are preferred. Similarly, polynucleotides encoding these polypeptide fragments are also preferred.

[221] The present invention further provides polypeptides having one or more residues deleted from the amino terminus of the amino acid sequence of a polypeptide disclosed herein (e.g., a polypeptide of SEQ ID NO:Y, a polypeptide as defined in columns 14 and 15 of Table 1A, a polypeptide encoded by the polynucleotide sequence contained in SEQ ID NO:X or the complement thereof, a polypeptide encoded by the portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2, a polypeptide encoded by the portion of SEQ ID NO:B as defined in column 6 of Table 1C, a polypeptide encoded by the cDNA contained in Clone ID NO:Z, and/or a mature polypeptide encoded by the cDNA contained in Clone ID NO:Z). In particular, N-terminal deletions may be described by the general formula m-

q, where q is a whole integer representing the total number of amino acid residues in a polypeptide of the invention (e.g., the polypeptide disclosed in SEQ ID NO:Y, the mature (secreted) portion of SEQ ID NO:Y as defined in columns 14 and 15 of Table 1A, or the polypeptide encoded by the portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2), and m is defined as any integer ranging from 2 to q-6. Polynucleotides encoding these polypeptides are also encompassed by the invention.

The present invention further provides polypeptides having one or more residues from the carboxy terminus of the amino acid sequence of a polypeptide disclosed herein (e.g., a polypeptide of SEQ ID NO:Y, the mature (secreted) portion of SEQ ID NO:Y as defined in columns 14 and 15 of Table 1A, a polypeptide encoded by the polynucleotide sequence contained in SEQ ID NO:X, a polypeptide encoded by the portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2, a polypeptide encoded by the portion of SEQ ID NO:B as defined in column 6 of Table 1C, a polypeptide encoded by the cDNA contained in Clone ID NO:Z, and/or a mature polypeptide encoded by the cDNA contained in Clone ID NO:Z). In particular, C-terminal deletions may be described by the general formula 1-n, where n is any whole integer ranging from 6 to q-1, and where n corresponds to the position of amino acid residue in a polypeptide of the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

In addition, any of the above described N- or C-terminal deletions can be combined to produce a N- and C-terminal deleted polypeptide. The invention also provides polypeptides having one or more amino acids deleted from both the amino and the carboxyl termini, which may be described generally as having residues m-n of a polypeptide encoded by SEQ ID NO:X (e.g., including, but not limited to, the preferred polypeptide disclosed as SEQ ID NO:Y, the mature (secreted) portion of SEQ ID NO:Y as defined in columns 14 and 15 of Table 1A, and the polypeptide encoded by the portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2), the cDNA contained in Clone ID NO:Z, and/or the complement thereof, where n and m are integers as described above. Polynucleotides encoding these polypeptides are also encompassed by the invention.

[224] Also as mentioned above, even if deletion of one or more amino acids from the C-terminus of a protein results in modification of loss of one or more biological functions of the protein, other functional activities (e.g., biological activities, ability to multimerize, ability to bind a ligand) may still be retained. For example the ability of the shortened mutein to induce and/or bind to antibodies which recognize the complete or mature forms of

the polypeptide generally will be retained when less than the majority of the residues of the complete or mature polypeptide are removed from the C-terminus. Whether a particular polypeptide lacking C-terminal residues of a complete polypeptide retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art. It is not unlikely that a mutein with a large number of deleted C-terminal amino acid residues may retain some biological or immunogenic activities. In fact, peptides composed of as few as six amino acid residues may often evoke an immune response.

[225] The present application is also directed to proteins containing polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to a polypeptide sequence set forth herein. In preferred embodiments, the application is directed to proteins containing polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to polypeptides having the amino acid sequence of the specific N- and C-terminal deletions. Polynucleotides encoding these polypeptides are also encompassed by the invention.

[226] Any polypeptide sequence encoded by, for example, the polynucleotide sequences set forth as SEQ ID NO:X or the complement thereof, (presented, for example, in Tables 1A and 2), the cDNA contained in Clone ID NO:Z, or the polynucleotide sequence as defined in column 6 of Table 1C, may be analyzed to determine certain preferred regions of the polypeptide. For example, the amino acid sequence of a polypeptide encoded by a polynucleotide sequence of SEQ ID NO:X (e.g., the polypeptide of SEQ ID NO:Y and the polypeptide encoded by the portion of SEQ ID NO:X as defined in columnns 8 and 9 of Table 2) or the cDNA contained in Clone ID NO:Z may be analyzed using the default parameters of the DNASTAR computer algorithm (DNASTAR, Inc., 1228 S. Park St., Madison, WI 53715 USA; http://www.dnastar.com/).

[227] Polypeptide regions that may be routinely obtained using the DNASTAR computer algorithm include, but are not limited to, Garnier-Robson alpha-regions, beta-regions, turn-regions, and coil-regions; Chou-Fasman alpha-regions, beta-regions, and turn-regions; Kyte-Doolittle hydrophilic regions and hydrophobic regions; Eisenberg alpha-and beta-amphipathic regions; Karplus-Schulz flexible regions; Emini surface-forming regions; and Jameson-Wolf regions of high antigenic index. Among highly preferred polynucleotides of the invention in this regard are those that encode polypeptides comprising regions that combine several structural features, such as several (e.g., 1, 2, 3 or 4) of the features set out above.

Additionally, Kyte-Doolittle hydrophilic regions and hydrophobic regions, Emini surface-forming regions, and Jameson-Wolf regions of high antigenic index (i.e., containing four or more contiguous amino acids having an antigenic index of greater than or equal to 1.5, as identified using the default parameters of the Jameson-Wolf program) can routinely be used to determine polypeptide regions that exhibit a high degree of potential for antigenicity. Regions of high antigenicity are determined from data by DNASTAR analysis by choosing values which represent regions of the polypeptide which are likely to be exposed on the surface of the polypeptide in an environment in which antigen recognition may occur in the process of initiation of an immune response.

[229] Preferred polypeptide fragments of the invention are fragments comprising, or alternatively, consisting of, an amino acid sequence that displays a functional activity (e.g. biological activity) of the polypeptide sequence of which the amino acid sequence is a fragment. By a polypeptide displaying a "functional activity" is meant a polypeptide capable of one or more known functional activities associated with a full-length protein, such as, for example, biological activity, antigenicity, immunogenicity, and/or multimerization, as described herein.

[230] Other preferred polypeptide fragments are biologically active fragments. Biologically active fragments are those exhibiting activity similar, but not necessarily identical, to an activity of the polypeptide of the present invention. The biological activity of the fragments may include an improved desired activity, or a decreased undesirable activity.

[231] In preferred embodiments, polypeptides of the invention comprise, or alternatively consist of, one, two, three, four, five or more of the antigenic fragments of the polypeptide of SEQ ID NO:Y, or portions thereof. Polynucleotides encoding these polypeptides are also encompassed by the invention.

Epitopes and Antibodies

[232] The present invention encompasses polypeptides comprising, or alternatively consisting of, an epitope of: the polypeptide sequence shown in SEQ ID NO:Y; a polypeptide sequence encoded by SEQ ID NO:X or the complementary strand thereto; the polypeptide sequence encoded by the portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2; the polypeptide sequence encoded by the portion of SEQ ID NO:B as defined in column 6 of Table 1C or the complement thereto; the polypeptide sequence encoded by

the cDNA contained in Clone ID NO:Z; or the polypeptide sequence encoded by a polynucleotide that hybridizes to the sequence of SEQ ID NO:X, the complement of the sequence of SEQ ID NO:X, the complement of a portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2, or the cDNA sequence contained in Clone ID NO:Z under stringent hybridization conditions or alternatively, under lower stringency hybridization as defined *supra*. The present invention further encompasses polynucleotide sequences encoding an epitope of a polypeptide sequence of the invention (such as, for example, the sequence disclosed in SEQ ID NO:X, or a fragment thereof), polynucleotide sequences of the complementary strand of a polynucleotide sequence encoding an epitope of the invention, and polynucleotide sequences which hybridize to the complementary strand under stringent hybridization conditions or alternatively, under lower stringency hybridization conditions defined *supra*.

[233] The term "epitopes," as used herein, refers to portions of a polypeptide having antigenic or immunogenic activity in an animal, preferably a mammal, and most preferably in a human. In a preferred embodiment, the present invention encompasses a polypeptide comprising an epitope, as well as the polynucleotide encoding this polypeptide. An "immunogenic epitope," as used herein, is defined as a portion of a protein that elicits an antibody response in an animal, as determined by any method known in the art, for example, by the methods for generating antibodies described *infra*. (See, for example, Geysen et al., Proc. Natl. Acad. Sci. USA 81:3998- 4002 (1983)). The term "antigenic epitope," as used herein, is defined as a portion of a protein to which an antibody can immunospecifically bind its antigen as determined by any method well known in the art, for example, by the immunoassays described herein. Immunospecific binding excludes non-specific binding but does not necessarily exclude cross- reactivity with other antigens. Antigenic epitopes need not necessarily be immunogenic.

[234] Fragments which function as epitopes may be produced by any conventional means. (See, e.g., Houghten, R. A., Proc. Natl. Acad. Sci. USA 82:5131-5135 (1985) further described in U.S. Patent No. 4,631,211.)

[235] In the present invention, antigenic epitopes preferably contain a sequence of at least 4, at least 5, at least 6, at least 7, more preferably at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 20, at least 25, at least 30, at least 40, at least 50, and, most preferably, between about 15 to about 30 amino acids. Preferred polypeptides comprising immunogenic or antigenic epitopes are at least 10, 15,

20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, or 100 amino acid residues in length. Additional non-exclusive preferred antigenic epitopes include the antigenic epitopes disclosed herein, as well as portions thereof. Antigenic epitopes are useful, for example, to raise antibodies, including monoclonal antibodies, that specifically bind the epitope. Preferred antigenic epitopes include the antigenic epitopes disclosed herein, as well as any combination of two, three, four, five or more of these antigenic epitopes. Antigenic epitopes can be used as the target molecules in immunoassays. (See, for instance, Wilson et al., Cell 37:767-778 (1984); Sutcliffe et al., Science 219:660-666 (1983)).

[236] Non-limiting examples of epitopes of polypeptides that can be used to generate antibodies of the invention include a polypeptide comprising, or alternatively consisting of, at least one, two, three, four, five, six or more of the portion(s) of SEQ ID NO:Y specified in column 7 of Table 1B. These polypeptide fragments have been determined to bear antigenic epitopes of the proteins of the invention by the analysis of the Jameson-Wolf antigenic index which is included in the DNAStar suite of computer programs. By "comprise" it is intended that a polypeptide contains at least one, two, three, four, five, six or more of the portion(s) of SEQ ID NO:Y shown in column 7 of Table 1B, but it may contain additional flanking residues on either the amino or carboxyl termini of the recited Such additional flanking sequences are preferably sequences naturally found portion. adjacent to the portion; i.e., contiguous sequence shown in SEQ ID NO:Y. The flanking sequence may, however, be sequences from a heterolgous polypeptide, such as from another protein described herein or from a heterologous polypeptide not described herein. In particular embodiments, epitope portions of a polypeptide of the invention comprise one, two, three, or more of the portions of SEQ ID NO:Y shown in column 7 of Table 1B.

[237] Similarly, immunogenic epitopes can be used, for example, to induce antibodies according to methods well known in the art. See, for instance, Sutcliffe et al., *supra*; Wilson et al., *supra*; Chow et al., Proc. Natl. Acad. Sci. USA 82:910-914; and Bittle et al., J. Gen. Virol. 66:2347-2354 (1985). Preferred immunogenic epitopes include the immunogenic epitopes disclosed herein, as well as any combination of two, three, four, five or more of these immunogenic epitopes. The polypeptides comprising one or more immunogenic epitopes may be presented for eliciting an antibody response together with a carrier protein, such as an albumin, to an animal system (such as rabbit or mouse), or, if the polypeptide is of sufficient length (at least about 25 amino acids), the polypeptide may be presented without a carrier. However, immunogenic epitopes comprising as few as 8 to 10

amino acids have been shown to be sufficient to raise antibodies capable of binding to, at the very least, linear epitopes in a denatured polypeptide (e.g., in Western blotting).

[238] Epitope-bearing polypeptides of the present invention may be used to induce antibodies according to methods well known in the art including, but not limited to, in vivo immunization, in vitro immunization, and phage display methods. See, e.g., Sutcliffe et al., supra; Wilson et al., supra, and Bittle et al., J. Gen. Virol., 66:2347-2354 (1985). If in vivo immunization is used, animals may be immunized with free peptide; however, anti-peptide antibody titer may be boosted by coupling the peptide to a macromolecular carrier, such as keyhole limpet hemacyanin (KLH) or tetanus toxoid. For instance, peptides containing cysteine residues may be coupled to a carrier using a linker such as maleimidobenzoyl- Nhydroxysuccinimide ester (MBS), while other peptides may be coupled to carriers using a more general linking agent such as glutaraldehyde. Animals such as rabbits, rats and mice are immunized with either free or carrier- coupled peptides, for instance, by intraperitoneal and/or intradermal injection of emulsions containing about 100 µg of peptide or carrier protein and Freund's adjuvant or any other adjuvant known for stimulating an immune response. Several booster injections may be needed, for instance, at intervals of about two weeks, to provide a useful titer of anti-peptide antibody which can be detected, for example, by ELISA assay using free peptide adsorbed to a solid surface. The titer of anti-peptide antibodies in serum from an immunized animal may be increased by selection of antipeptide antibodies, for instance, by adsorption to the peptide on a solid support and elution of the selected antibodies according to methods well known in the art.

As one of skill in the art will appreciate, and as discussed above, the polypeptides of the present invention (e.g., those comprising an immunogenic or antigenic epitope) can be fused to heterologous polypeptide sequences. For example, polypeptides of the present invention (including fragments or variants thereof), may be fused with the constant domain of immunoglobulins (IgA, IgE, IgG, IgM), or portions thereof (CH1, CH2, CH3, or any combination thereof and portions thereof, resulting in chimeric polypeptides. By way of another non-limiting example, polypeptides and/or antibodies of the present invention (including fragments or variants thereof) may be fused with albumin (including but not limited to recombinant human serum albumin or fragments or variants thereof (see, e.g., U.S. Patent No. 5,876,969, issued March 2, 1999, EP Patent 0 413 622, and U.S. Patent No. 5,766,883, issued June 16, 1998, herein incorporated by reference in their entirety)). In a preferred embodiment, polypeptides and/or antibodies of the present invention (including

fragments or variants thereof) are fused with the mature form of human serum albumin (i.e., amino acids 1 – 585 of human serum albumin as shown in Figures 1 and 2 of EP Patent 0 322 094) which is herein incorporated by reference in its entirety. In another preferred embodiment, polypeptides and/or antibodies of the present invention (including fragments or variants thereof) are fused with polypeptide fragments comprising, or alternatively consisting of, amino acid residues 1-z of human serum albumin, where z is an integer from 369 to 419, as described in U.S. Patent 5,766,883 herein incorporated by reference in its entirety. Polypeptides and/or antibodies of the present invention (including fragments or variants thereof) may be fused to either the N- or C-terminal end of the heterologous protein (e.g., immunoglobulin Fc polypeptide or human serum albumin polypeptide). Polynucleotides encoding fusion proteins of the invention are also encompassed by the invention.

Such fusion proteins as those described above may facilitate purification and may [240] increase half-life in vivo. This has been shown for chimeric proteins consisting of the first two domains of the human CD4-polypeptide and various domains of the constant regions of the heavy or light chains of mammalian immunoglobulins. See, e.g., EP 394,827; Traunecker et al., Nature, 331:84-86 (1988). Enhanced delivery of an antigen across the epithelial barrier to the immune system has been demonstrated for antigens (e.g., insulin) conjugated to an FcRn binding partner such as IgG or Fc fragments (see, e.g., PCT Publications WO 96/22024 and WO 99/04813). IgG fusion proteins that have a disulfidelinked dimeric structure due to the IgG portion desulfide bonds have also been found to be more efficient in binding and neutralizing other molecules than monomeric polypeptides or fragments thereof alone. See, e.g., Fountoulakis et al., J. Biochem., 270:3958-3964 (1995). Nucleic acids encoding the above epitopes can also be recombined with a gene of interest as an epitope tag (e.g., the hemagglutinin (HA) tag or flag tag) to aid in detection and purification of the expressed polypeptide. For example, a system described by Janknecht et al. allows for the ready purification of non-denatured fusion proteins expressed in human cell lines (Janknecht et al., 1991, Proc. Natl. Acad. Sci. USA 88:8972-897). In this system, the gene of interest is subcloned into a vaccinia recombination plasmid such that the open reading frame of the gene is translationally fused to an aminoterminal tag consisting of six histidine residues. The tag serves as a matrix binding domain for the fusion protein. Extracts from cells infected with the recombinant vaccinia virus are loaded onto Ni2+ nitriloacetic acid-agarose column and histidine-tagged proteins can be selectively eluted with imidazole-containing buffers.

Fusion Proteins

Any polypeptide of the present invention can be used to generate fusion proteins. For example, the polypeptide of the present invention, when fused to a second protein, can be used as an antigenic tag. Antibodies raised against the polypeptide of the present invention can be used to indirectly detect the second protein by binding to the polypeptide. Moreover, because secreted proteins target cellular locations based on trafficking signals, polypeptides of the present invention which are shown to be secreted can be used as targeting molecules once fused to other proteins.

[242] Examples of domains that can be fused to polypeptides of the present invention include not only heterologous signal sequences, but also other heterologous functional regions. The fusion does not necessarily need to be direct, but may occur through linker sequences.

[243] In certain preferred embodiments, proteins of the invention are fusion proteins comprising an amino acid sequence that is an N and/or C- terminal deletion of a polypeptide of the invention. In preferred embodiments, the invention is directed to a fusion protein comprising an amino acid sequence that is at least 90%, 95%, 96%, 97%, 98% or 99% identical to a polypeptide sequence of the invention. Polynucleotides encoding these proteins are also encompassed by the invention.

[244] Moreover, fusion proteins may also be engineered to improve characteristics of the polypeptide of the present invention. For instance, a region of additional amino acids, particularly charged amino acids, may be added to the N-terminus of the polypeptide to improve stability and persistence during purification from the host cell or subsequent handling and storage. Also, peptide moieties may be added to the polypeptide to facilitate purification. Such regions may be removed prior to final preparation of the polypeptide. The addition of peptide moieties to facilitate handling of polypeptides are familiar and routine techniques in the art.

[245] As one of skill in the art will appreciate that, as discussed above, polypeptides of the present invention, and epitope-bearing fragments thereof, can be combined with heterologous polypeptide sequences. For example, the polypeptides of the present invention may be fused with heterologous polypeptide sequences, for example, the

polypeptides of the present invention may be fused with the constant domain of immunoglobulins (IgA, IgE, IgG, IgM) or portions thereof (CH1, CH2, CH3, and any combination thereof, including both entire domains and portions thereof), or albumin (including, but not limited to, native or recombinant human albumin or fragments or variants thereof (see, e.g., U.S. Patent No. 5,876,969, issued March 2, 1999, EP Patent 0 413 622, and U.S. Patent No. 5,766,883, issued June 16, 1998, herein incorporated by reference in their entirety)), resulting in chimeric polypeptides. For example, EP-A-O 464 533 (Canadian counterpart 2045869) discloses fusion proteins comprising various portions of constant region of immunoglobulin molecules together with another human protein or part thereof. In many cases, the Fc part in a fusion protein is beneficial in therapy and diagnosis, and thus can result in, for example, improved pharmacokinetic properties (EP-A 0232 262). Alternatively, deleting the Fc part after the fusion protein has been expressed, detected, and purified, would be desired. For example, the Fc portion may hinder therapy and diagnosis if the fusion protein is used as an antigen for immunizations. In drug discovery, for example, human proteins, such as hIL-5, have been fused with Fc portions for the purpose of high-throughput screening assays to identify antagonists of hIL-5. See, D. Bennett et al., J. Molecular Recognition 8:52-58 (1995); K. Johanson et al., J. Biol. Chem. 270:9459-9471 (1995).

[246] Moreover, the polypeptides of the present invention can be fused to marker sequences, such as a polypeptide which facilitates purification of the fused polypeptide. In preferred embodiments, the marker amino acid sequence is a hexa-histidine peptide, such as the tag provided in a pQE vector (QIAGEN, Inc., 9259 Eton Avenue, Chatsworth, CA, 91311), among others, many of which are commercially available. As described in Gentz et al., Proc. Natl. Acad. Sci. USA 86:821-824 (1989), for instance, hexa-histidine provides for convenient purification of the fusion protein. Another peptide tag useful for purification, the "HA" tag, corresponds to an epitope derived from the influenza hemagglutinin protein (Wilson et al., Cell 37:767 (1984)).

[247] Additional fusion proteins of the invention may be generated through the techniques of gene-shuffling, motif-shuffling, exon-shuffling, and/or codon-shuffling (collectively referred to as "DNA shuffling"). DNA shuffling may be employed to modulate the activities of polypeptides of the invention, such methods can be used to generate polypeptides with altered activity, as well as agonists and antagonists of the polypeptides. See, generally, U.S. Patent Nos. 5,605,793; 5,811,238; 5,830,721; 5,834,252;

and 5,837,458, and Patten et al., Curr. Opinion Biotechnol. 8:724-33 (1997); Harayama, Trends Biotechnol. 16(2):76-82 (1998); Hansson, et al., J. Mol. Biol. 287:265-76 (1999); and Lorenzo and Blasco, Biotechniques 24(2):308- 13 (1998) (each of these patents and publications are hereby incorporated by reference in its entirety). In one embodiment, alteration of polynucleotides corresponding to SEQ ID NO:X and the polypeptides encoded by these polynucleotides may be achieved by DNA shuffling. DNA shuffling involves the assembly of two or more DNA segments by homologous or site-specific recombination to generate variation in the polynucleotide sequence. In another embodiment, polynucleotides of the invention, or the encoded polypeptides, may be altered by being subjected to random mutagenesis by error-prone PCR, random nucleotide insertion or other methods prior to recombination. In another embodiment, one or more components, motifs, sections, parts, domains, fragments, etc., of a polynucleotide encoding a polypeptide of the invention may be recombined with one or more components, motifs, sections, parts, domains, fragments, etc. of one or more heterologous molecules.

[248] Thus, any of these above fusions can be engineered using the polynucleotides or the polypeptides of the present invention.

Recombinant and Synthetic Production of Polypeptides of the Invention

[249] The present invention also relates to vectors containing the polynucleotide of the present invention, host cells, and the production of polypeptides by synthetic and recombinant techniques. The vector may be, for example, a phage, plasmid, viral, or retroviral vector. Retroviral vectors may be replication competent or replication defective. In the latter case, viral propagation generally will occur only in complementing host cells.

[250] The polynucleotides of the invention may be joined to a vector containing a selectable marker for propagation in a host. Generally, a plasmid vector is introduced in a precipitate, such as a calcium phosphate precipitate, or in a complex with a charged lipid. If the vector is a virus, it may be packaged in vitro using an appropriate packaging cell line and then transduced into host cells.

[251] The polynucleotide insert should be operatively linked to an appropriate promoter, such as the phage lambda PL promoter, the E. coli lac, trp, phoA and tac promoters, the SV40 early and late promoters and promoters of retroviral LTRs, to name a few. Other suitable promoters will be known to the skilled artisan. The expression constructs will further contain sites for transcription initiation, termination, and, in the

transcribed region, a ribosome binding site for translation. The coding portion of the transcripts expressed by the constructs will preferably include a translation initiating codon at the beginning and a termination codon (UAA, UGA or UAG) appropriately positioned at the end of the polypeptide to be translated.

[252] As indicated, the expression vectors will preferably include at least one selectable marker. Such markers include dihydrofolate reductase, G418, glutamine synthase, or neomycin resistance for eukaryotic cell culture, and tetracycline, kanamycin or ampicillin resistance genes for culturing in E. coli and other bacteria. Representative examples of appropriate hosts include, but are not limited to, bacterial cells, such as E. coli, Streptomyces and Salmonella typhimurium cells; fungal cells, such as yeast cells (e.g., Saccharomyces cerevisiae or Pichia pastoris (ATCC Accession No. 201178)); insect cells such as Drosophila S2 and Spodoptera Sf9 cells; animal cells such as CHO, COS, 293, and Bowes melanoma cells; and plant cells. Appropriate culture mediums and conditions for the above-described host cells are known in the art.

Among vectors preferred for use in bacteria include pQE70, pQE60 and pQE-9, available from QIAGEN, Inc.; pBluescript vectors, Phagescript vectors, pNH8A, pNH16a, pNH18A, pNH46A, available from Stratagene Cloning Systems, Inc.; and ptrc99a, pKK223-3, pKK233-3, pDR540, pRIT5 available from Pharmacia Biotech, Inc. Among preferred eukaryotic vectors are pWLNEO, pSV2CAT, pOG44, pXT1 and pSG available from Stratagene; and pSVK3, pBPV, pMSG and pSVL available from Pharmacia. Preferred expression vectors for use in yeast systems include, but are not limited to pYES2, pYD1, pTEF1/Zeo, pYES2/GS, pPICZ, pGAPZ, pGAPZalph, pPIC9, pPIC3.5, pHIL-D2, pHIL-S1, pPIC3.5K, pPIC9K, and PAO815 (all available from Invitrogen, Carlbad, CA). Other suitable vectors will be readily apparent to the skilled artisan.

Vectors which use glutamine synthase (GS) or DHFR as the selectable markers can be amplified in the presence of the drugs methionine sulphoximine or methotrexate, respectively. An advantage of glutamine synthase based vectors are the availabilty of cell lines (e.g., the murine myeloma cell line, NS0) which are glutamine synthase negative. Glutamine synthase expression systems can also function in glutamine synthase expressing cells (e.g., Chinese Hamster Ovary (CHO) cells) by providing additional inhibitor to prevent the functioning of the endogenous gene. A glutamine synthase expression system and components thereof are detailed in PCT publications: WO87/04462; WO86/05807; WO89/01036; WO89/10404; and WO91/06657, which are hereby incorporated in their

entireties by reference herein. Additionally, glutamine synthase expression vectors can be obtained from Lonza Biologics, Inc. (Portsmouth, NH). Expression and production of monoclonal antibodies using a GS expression system in murine myeloma cells is described in Bebbington *et al.*, *Bio/technology* 10:169(1992) and in Biblia and Robinson *Biotechnol. Prog.* 11:1 (1995) which are herein incorporated by reference.

The present invention also relates to host cells containing the above-described [255] vector constructs described herein, and additionally encompasses host cells containing nucleotide sequences of the invention that are operably associated with one or more heterologous control regions (e.g., promoter and/or enhancer) using techniques known of in The host cell can be a higher eukaryotic cell, such as a mammalian cell (e.g., a the art. human derived cell), or a lower eukaryotic cell, such as a yeast cell, or the host cell can be a prokaryotic cell, such as a bacterial cell. A host strain may be chosen which modulates the expression of the inserted gene sequences, or modifies and processes the gene product in the specific fashion desired. Expression from certain promoters can be elevated in the presence of certain inducers; thus expression of the genetically engineered polypeptide may Furthermore, different host cells have characteristics and specific be controlled. mechanisms for the translational and post-translational processing and modification (e.g., phosphorylation, cleavage) of proteins. Appropriate cell lines can be chosen to ensure the desired modifications and processing of the foreign protein expressed.

[256] Introduction of the nucleic acids and nucleic acid constructs of the invention into the host cell can be effected by calcium phosphate transfection, DEAE-dextran mediated transfection, cationic lipid-mediated transfection, electroporation, transduction, infection, or other methods. Such methods are described in many standard laboratory manuals, such as Davis et al., Basic Methods In Molecular Biology (1986). It is specifically contemplated that the polypeptides of the present invention may in fact be expressed by a host cell lacking a recombinant vector.

[257] In addition to encompassing host cells containing the vector constructs discussed herein, the invention also encompasses primary, secondary, and immortalized host cells of vertebrate origin, particularly mammalian origin, that have been engineered to delete or replace endogenous genetic material (e.g., the coding sequence), and/or to include genetic material (e.g., heterologous polynucleotide sequences) that is operably associated with polynucleotides of the invention, and which activates, alters, and/or amplifies endogenous polynucleotides. For example, techniques known in the art may be used to operably

associate heterologous control regions (e.g., promoter and/or enhancer) and endogenous polynucleotide sequences via homologous recombination (see, e.g., US Patent Number 5,641,670, issued June 24, 1997; International Publication Number WO 96/29411; International Publication Number WO 94/12650; Koller *et al.*, *Proc. Natl. Acad. Sci. USA* 86:8932-8935 (1989); and Zijlstra *et al.*, *Nature* 342:435-438 (1989), the disclosures of each of which are incorporated by reference in their entireties).

[258] Polypeptides of the invention can be recovered and purified from recombinant cell cultures by well-known methods including ammonium sulfate or ethanol precipitation, acid extraction, anion or cation exchange chromatography, phosphocellulose chromatography, hydrophobic interaction chromatography, affinity chromatography, hydroxylapatite chromatography and lectin chromatography. Most preferably, high performance liquid chromatography ("HPLC") is employed for purification.

[259] Polypeptides of the present invention can also be recovered from: products purified from natural sources, including bodily fluids, tissues and cells, whether directly isolated or cultured; products of chemical synthetic procedures; and products produced by recombinant techniques from a prokaryotic or eukaryotic host, including, for example, bacterial, yeast, higher plant, insect, and mammalian cells. Depending upon the host employed in a recombinant production procedure, the polypeptides of the present invention may be glycosylated or may be non-glycosylated. In addition, polypeptides of the invention may also include an initial modified methionine residue, in some cases as a result of host-mediated processes. Thus, it is well known in the art that the N-terminal methionine encoded by the translation initiation codon generally is removed with high efficiency from any protein after translation in all eukaryotic cells. While the N-terminal methionine on most proteins also is efficiently removed in most prokaryotes, for some proteins, this prokaryotic removal process is inefficient, depending on the nature of the amino acid to which the N-terminal methionine is covalently linked.

[260] In one embodiment, the yeast *Pichia pastoris* is used to express polypeptides of the invention in a eukaryotic system. *Pichia pastoris* is a methylotrophic yeast which can metabolize methanol as its sole carbon source. A main step in the methanol metabolization pathway is the oxidation of methanol to formaldehyde using O₂. This reaction is catalyzed by the enzyme alcohol oxidase. In order to metabolize methanol as its sole carbon source, *Pichia pastoris* must generate high levels of alcohol oxidase due, in part, to the relatively

low affinity of alcohol oxidase for O₂. Consequently, in a growth medium depending on methanol as a main carbon source, the promoter region of one of the two alcohol oxidase genes (AOXI) is highly active. In the presence of methanol, alcohol oxidase produced from the AOXI gene comprises up to approximately 30% of the total soluble protein in Pichia pastoris. See Ellis, S.B., et al., Mol. Cell. Biol. 5:1111-21 (1985); Koutz, P.J, et al., Yeast 5:167-77 (1989); Tschopp, J.F., et al., Nucl. Acids Res. 15:3859-76 (1987). Thus, a heterologous coding sequence, such as, for example, a polynucleotide of the present invention, under the transcriptional regulation of all or part of the AOXI regulatory sequence is expressed at exceptionally high levels in Pichia yeast grown in the presence of methanol.

[261] In one example, the plasmid vector pPIC9K is used to express DNA encoding a polypeptide of the invention, as set forth herein, in a *Pichea* yeast system essentially as described in "*Pichia* Protocols: Methods in Molecular Biology," D.R. Higgins and J. Cregg, eds. The Humana Press, Totowa, NJ, 1998. This expression vector allows expression and secretion of a polypeptide of the invention by virtue of the strong *AOX1* promoter linked to the *Pichia pastoris* alkaline phosphatase (PHO) secretory signal peptide (i.e., leader) located upstream of a multiple cloning site.

[262] Many other yeast vectors could be used in place of pPIC9K, such as, pYES2, pYD1, pTEF1/Zeo, pYES2/GS, pPICZ, pGAPZ, pGAPZalpha, pPIC9, pPIC3.5, pHIL-D2, pHIL-S1, pPIC3.5K, and PAO815, as one skilled in the art would readily appreciate, as long as the proposed expression construct provides appropriately located signals for transcription, translation, secretion (if desired), and the like, including an in-frame AUG as required.

[263] In another embodiment, high-level expression of a heterologous coding sequence, such as, for example, a polynucleotide of the present invention, may be achieved by cloning the heterologous polynucleotide of the invention into an expression vector such as, for example, pGAPZ or pGAPZalpha, and growing the yeast culture in the absence of methanol.

[264] In addition to encompassing host cells containing the vector constructs discussed herein, the invention also encompasses primary, secondary, and immortalized host cells of vertebrate origin, particularly mammalian origin, that have been engineered to delete or

replace endogenous genetic material (e.g., coding sequence), and/or to include genetic material (e.g., heterologous polynucleotide sequences) that is operably associated with polynucleotides of the invention, and which activates, alters, and/or amplifies endogenous polynucleotides. For example, techniques known in the art may be used to operably associate heterologous control regions (e.g., promoter and/or enhancer) and endogenous polynucleotide sequences via homologous recombination (see, e.g., U.S. Patent No. 5,641,670, issued June 24, 1997; International Publication No. WO 96/29411, published September 26, 1996; International Publication No. WO 94/12650, published August 4, 1994; Koller et al., Proc. Natl. Acad. Sci. USA 86:8932-8935 (1989); and Zijlstra et al., Nature 342:435-438 (1989), the disclosures of each of which are incorporated by reference in their entireties).

In addition, polypeptides of the invention can be chemically synthesized using [265] techniques known in the art (e.g., see Creighton, 1983, Proteins: Structures and Molecular Principles, W.H. Freeman & Co., N.Y., and Hunkapiller et al., Nature, 310:105-111 (1984)). For example, a polypeptide corresponding to a fragment of a polypeptide can be synthesized by use of a peptide synthesizer. Furthermore, if desired, nonclassical amino acids or chemical amino acid analogs can be introduced as a substitution or addition into the polypeptide sequence. Non-classical amino acids include, but are not limited to, to the Disomers of the common amino acids, 2,4-diaminobutyric acid, a-amino isobutyric acid, 4aminobutyric acid, Abu, 2-amino butyric acid, g-Abu, e-Ahx, 6-amino hexanoic acid, Aib, 2-amino isobutyric acid, 3-amino propionic acid, ornithine, norleucine, norvaline, hydroxyproline, sarcosine, citrulline, homocitrulline, cysteic acid, t-butylglycine, tbutylalanine, phenylglycine, cyclohexylalanine, b-alanine, fluoro-amino acids, designer amino acids such as b-methyl amino acids, Ca-methyl amino acids, Na-methyl amino acids, and amino acid analogs in general. Furthermore, the amino acid can be D (dextrorotary) or L (levorotary).

[266] The invention encompasses polypeptides of the present invention which are differentially modified during or after translation, e.g., by glycosylation, acetylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to an antibody molecule or other cellular ligand, etc. Any of numerous chemical modifications may be carried out by known techniques, including but not limited, to specific chemical cleavage by cyanogen bromide, trypsin, chymotrypsin, papain, V8 protease, NaBH₄; acetylation, formylation, oxidation, reduction; metabolic

synthesis in the presence of tunicamycin; etc.

[267] Additional post-translational modifications encompassed by the invention include, for example, e.g., N-linked or O-linked carbohydrate chains, processing of N-terminal or C-terminal ends), attachment of chemical moieties to the amino acid backbone, chemical modifications of N-linked or O-linked carbohydrate chains, and addition or deletion of an N-terminal methionine residue as a result of procaryotic host cell expression. The polypeptides may also be modified with a detectable label, such as an enzymatic, fluorescent, isotopic or affinity label to allow for detection and isolation of the protein.

Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, beta-galactosidase, or acetylcholinesterase; examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes luminol; examples of bioluminescent materials include luciferase, luciferin, and aequorin; and examples of suitable radioactive material include iodine (121 I, 123 I, 125 I, 131 I), carbon (14C), sulfur (35S), tritium (3H), indium (111 In, 112 In, 113 In, 115 I

In specific embodiments, a polypeptide of the present invention or fragment or [269] variant thereof is attached to macrocyclic chelators that associate with radiometal ions, including but not limited to, ¹⁷⁷Lu, ⁹⁰Y, ¹⁶⁶Ho, and ¹⁵³Sm, to polypeptides. In a preferred embodiment, the radiometal ion associated with the macrocyclic chelators is ¹¹¹In. another preferred embodiment, the radiometal ion associated with the macrocyclic chelator ⁹⁰Y. macrocyclic chelator is is In specific embodiments, the 1,4,7,10acid tetraazacyclododecane-N,N',N",N"'-tetraacetic (DOTA). In other specific embodiments, DOTA is attached to an antibody of the invention or fragment thereof via a Examples of linker molecules useful for conjugating DOTA to a polypeptide are commonly known in the art - see, for example, DeNardo et al., Clin Cancer Res. 4(10):2483-90 (1998); Peterson et al., Bioconjug. Chem. 10(4):553-7 (1999); and Zimmerman et al, Nucl. Med. Biol. 26(8):943-50 (1999); which are hereby incorporated by reference in their entirety.

As mentioned, the proteins of the invention may be modified by either natural [270] processes, such as posttranslational processing, or by chemical modification techniques which are well known in the art. It will be appreciated that the same type of modification may be present in the same or varying degrees at several sites in a given polypeptide. Polypeptides of the invention may be branched, for example, as a result of ubiquitination, and they may be cyclic, with or without branching. Cyclic, branched, and branched cyclic polypeptides may result from posttranslation natural processes or may be made by synthetic Modifications include acetylation, acylation, ADP-ribosylation, amidation, methods. covalent attachment of flavin, covalent attachment of a heme moiety, covalent attachment of a nucleotide or nucleotide derivative, covalent attachment of a lipid or lipid derivative, covalent attachment of phosphotidylinositol, cross-linking, cyclization, disulfide bond formation, demethylation, formation of covalent cross-links, formation of cysteine, formation of pyroglutamate, formylation, gamma-carboxylation, glycosylation, GPI anchor formation, hydroxylation, iodination, methylation, myristoylation, oxidation, pegylation, proteolytic processing, phosphorylation, prenylation, racemization, selenoylation, sulfation, transfer-RNA mediated addition of amino acids to proteins such as arginylation, and ubiquitination. (See, for instance, PROTEINS - STRUCTURE AND MOLECULAR PROPERTIES, 2nd Ed., T. E. Creighton, W. H. Freeman and Company, New York (1993); POSTTRANSLATIONAL COVALENT MODIFICATION OF PROTEINS, B. C. Johnson, Ed., Academic Press, New York, pgs. 1-12 (1983); Seifter et al., Meth. Enzymol. 182:626-646 (1990); Rattan et al., Ann. N.Y. Acad. Sci. 663:48-62 (1992)).

[271] Also provided by the invention are chemically modified derivatives of the polypeptides of the invention which may provide additional advantages such as increased solubility, stability and circulating time of the polypeptide, or decreased immunogenicity (see U.S. Patent No. 4,179,337). The chemical moieties for derivitization may be selected from water soluble polymers such as polyethylene glycol, ethylene glycol/propylene glycol copolymers, carboxymethylcellulose, dextran, polyvinyl alcohol and the like. The polypeptides may be modified at random positions within the molecule, or at predetermined positions within the molecule and may include one, two, three or more attached chemical moieties.

[272] The polymer may be of any molecular weight, and may be branched or unbranched. For polyethylene glycol, the preferred molecular weight is between about 1 kDa and about 100 kDa (the term "about" indicating that in preparations of polyethylene

glycol, some molecules will weigh more, some less, than the stated molecular weight) for ease in handling and manufacturing. Other sizes may be used, depending on the desired therapeutic profile (e.g., the duration of sustained release desired, the effects, if any on biological activity, the ease in handling, the degree or lack of antigenicity and other known effects of the polyethylene glycol to a therapeutic protein or analog). For example, the polyethylene glycol may have an average molecular weight of about 200, 500, 1000, 1500, 2000, 2500, 3000, 3500, 4000, 4500, 5000, 5500, 6000, 6500, 7000, 7500, 8000, 8500, 9000, 9500, 10,000, 10,500, 11,000, 11,500, 12,000, 12,500, 13,000, 13,500, 14,000, 14,500, 15,000, 15,500, 16,000, 16,500, 17,000, 17,500, 18,000, 18,500, 19,000, 19,500, 20,000, 25,000, 30,000, 35,000, 40,000, 45,000, 50,000, 55,000, 60,000, 65,000, 70,000, 75,000, 80,000, 85,000, 90,000, 95,000, or 100,000 kDa.

[273] As noted above, the polyethylene glycol may have a branched structure. Branched polyethylene glycols are described, for example, in U.S. Patent No. 5,643,575; Morpurgo et al., Appl. Biochem. Biotechnol. 56:59-72 (1996); Vorobjev et al., Nucleosides Nucleotides 18:2745-2750 (1999); and Caliceti et al., Bioconjug. Chem. 10:638-646 (1999), the disclosures of each of which are incorporated herein by reference.

The polyethylene glycol molecules (or other chemical moieties) should be [274] attached to the protein with consideration of effects on functional or antigenic domains of the protein. There are a number of attachment methods available to those skilled in the art, such as, for example, the method disclosed in EP 0 401 384 (coupling PEG to G-CSF), herein incorporated by reference; see also Malik et al., Exp. Hematol. 20:1028-1035 (1992), reporting pegylation of GM-CSF using tresyl chloride. For example, polyethylene glycol may be covalently bound through amino acid residues via a reactive group, such as a free amino or carboxyl group. Reactive groups are those to which an activated polyethylene glycol molecule may be bound. The amino acid residues having a free amino group may include lysine residues and the N-terminal amino acid residues; those having a free carboxyl group may include aspartic acid residues glutamic acid residues and the C-terminal amino acid residue. Sulfhydryl groups may also be used as a reactive group for Preferred for therapeutic purposes is attaching the polyethylene glycol molecules. attachment at an amino group, such as attachment at the N-terminus or lysine group.

[275] As suggested above, polyethylene glycol may be attached to proteins via linkage to any of a number of amino acid residues. For example, polyethylene glycol can be linked to proteins via covalent bonds to lysine, histidine, aspartic acid, glutamic acid, or cysteine

residues. One or more reaction chemistries may be employed to attach polyethylene glycol to specific amino acid residues (e.g., lysine, histidine, aspartic acid, glutamic acid, or cysteine) of the protein or to more than one type of amino acid residue (e.g., lysine, histidine, aspartic acid, glutamic acid, cysteine and combinations thereof) of the protein.

[276] One may specifically desire proteins chemically modified at the N-terminus. Using polyethylene glycol as an illustration of the present composition, one may select from a variety of polyethylene glycol molecules (by molecular weight, branching, etc.), the proportion of polyethylene glycol molecules to protein (polypeptide) molecules in the reaction mix, the type of pegylation reaction to be performed, and the method of obtaining the selected N-terminally pegylated protein. The method of obtaining the N-terminally pegylated preparation (i.e., separating this moiety from other monopegylated moieties if necessary) may be by purification of the N-terminally pegylated material from a population of pegylated protein molecules. Selective proteins chemically modified at the N-terminus modification may be accomplished by reductive alkylation which exploits differential reactivity of different types of primary amino groups (lysine versus the N-terminal) available for derivatization in a particular protein. Under the appropriate reaction conditions, substantially selective derivatization of the protein at the N-terminus with a carbonyl group containing polymer is achieved.

[277] As indicated above, pegylation of the proteins of the invention may be accomplished by any number of means. For example, polyethylene glycol may be attached to the protein either directly or by an intervening linker. Linkerless systems for attaching polyethylene glycol to proteins are described in Delgado et al., Crit. Rev. Thera. Drug Carrier Sys. 9:249-304 (1992); Francis et al., Intern. J. of Hematol. 68:1-18 (1998); U.S. Patent No. 4,002,531; U.S. Patent No. 5,349,052; WO 95/06058; and WO 98/32466, the disclosures of each of which are incorporated herein by reference.

[278] One system for attaching polyethylene glycol directly to amino acid residues of proteins without an intervening linker employs tresylated MPEG, which is produced by the modification of monmethoxy polyethylene glycol (MPEG) using tresylchloride (ClSO₂CH₂CF₃). Upon reaction of protein with tresylated MPEG, polyethylene glycol is directly attached to amine groups of the protein. Thus, the invention includes protein-polyethylene glycol conjugates produced by reacting proteins of the invention with a polyethylene glycol molecule having a 2,2,2-trifluoreothane sulphonyl group.

[279] Polyethylene glycol can also be attached to proteins using a number of different intervening linkers. For example, U.S. Patent No. 5,612,460, the entire disclosure of which is incorporated herein by reference, discloses urethane linkers for connecting polyethylene glycol to proteins. Protein-polyethylene glycol conjugates wherein the polyethylene glycol is attached to the protein by a linker can also be produced by reaction of proteins with compounds such MPEG-succinimidylsuccinate, **MPEG** activated with 1,1'-carbonyldiimidazole, MPEG-2,4,5-trichloropenylcarbonate, MPEG-pnitrophenolcarbonate, and various MPEG-succinate derivatives. A number of additional polyethylene glycol derivatives and reaction chemistries for attaching polyethylene glycol to proteins are described in International Publication No. WO 98/32466, the entire disclosure of which is incorporated herein by reference. Pegylated protein products produced using the reaction chemistries set out herein are included within the scope of the invention.

[280] The number of polyethylene glycol moieties attached to each protein of the invention (i.e., the degree of substitution) may also vary. For example, the pegylated proteins of the invention may be linked, on average, to 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 15, 17, 20, or more polyethylene glycol molecules. Similarly, the average degree of substitution within ranges such as 1-3, 2-4, 3-5, 4-6, 5-7, 6-8, 7-9, 8-10, 9-11, 10-12, 11-13, 12-14, 13-15, 14-16, 15-17, 16-18, 17-19, or 18-20 polyethylene glycol moieties per protein molecule. Methods for determining the degree of substitution are discussed, for example, in Delgado et al., Crit. Rev. Thera. Drug Carrier Sys. 9:249-304 (1992).

Synthesis and recombinant cell cultures by standard methods which include, but are not limited to, ammonium sulfate or ethanol precipitation, acid extraction, anion or cation exchange chromatography, phosphocellulose chromatography, hydrophobic interaction chromatography, affinity chromatography, hydroxylapatite chromatography and lectin chromatography. Most preferably, high performance liquid chromatography ("HPLC") is employed for purification. Well known techniques for refolding protein may be employed to regenerate active conformation when the polypeptide is denatured during isolation and/or purification.

[282] The polypeptides of the invention may be in monomers or multimers (i.e., dimers, trimers, tetramers and higher multimers). Accordingly, the present invention relates to monomers and multimers of the polypeptides of the invention, their preparation, and

compositions (preferably, Therapeutics) containing them. In specific embodiments, the polypeptides of the invention are monomers, dimers, trimers or tetramers. In additional embodiments, the multimers of the invention are at least dimers, at least trimers, or at least tetramers.

[283] Multimers encompassed by the invention may be homomers or heteromers. As used herein, the term homomer refers to a multimer containing only polypeptides corresponding to a protein of the invention (e.g., the amino acid sequence of SEQ ID NO:Y, an amino acid sequence encoded by SEQ ID NO:X or the complement of SEQ ID NO:X, the amino acid sequence encoded by the portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2, and/or an amino acid sequence encoded by cDNA contained in Clone ID NO:Z (including fragments, variants, splice variants, and fusion proteins, corresponding to these as described herein)). These homomers may contain polypeptides having identical or different amino acid sequences. In a specific embodiment, a homomer of the invention is a multimer containing only polypeptides having an identical amino acid sequence. In another specific embodiment, a homomer of the invention is a multimer containing polypeptides having different amino acid sequences. In specific embodiments, the multimer of the invention is a homodimer (e.g., containing two polypeptides having identical or different amino acid sequences) or a homotrimer (e.g., containing three polypeptides having identical and/or different amino acid sequences). In additional embodiments, the homomeric multimer of the invention is at least a homodimer, at least a homotrimer, or at least a homotetramer.

[284] As used herein, the term heteromer refers to a multimer containing one or more heterologous polypeptides (i.e., polypeptides of different proteins) in addition to the polypeptides of the invention. In a specific embodiment, the multimer of the invention is a heterodimer, a heterotrimer, or a heterotetramer. In additional embodiments, the heteromeric multimer of the invention is at least a heterodimer, at least a heterotrimer, or at least a heterotetramer.

[285] Multimers of the invention may be the result of hydrophobic, hydrophilic, ionic and/or covalent associations and/or may be indirectly linked by, for example, liposome formation. Thus, in one embodiment, multimers of the invention, such as, for example, homodimers or homotrimers, are formed when polypeptides of the invention contact one another in solution. In another embodiment, heteromultimers of the invention, such as, for example, heterotrimers or heterotetramers, are formed when polypeptides of the invention

contact antibodies to the polypeptides of the invention (including antibodies to the heterologous polypeptide sequence in a fusion protein of the invention) in solution. In other embodiments, multimers of the invention are formed by covalent associations with and/or between the polypeptides of the invention. Such covalent associations may involve one or more amino acid residues contained in the polypeptide sequence (e.g., that recited in SEQ ID NO:Y, encoded by the portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2, and/or encoded by the cDNA contained in Clone ID NO:Z). In one instance, the covalent associations are cross-linking between cysteine residues located within the polypeptide sequences which interact in the native (i.e., naturally occurring) polypeptide. In another instance, the covalent associations are the consequence of chemical or recombinant manipulation. Alternatively, such covalent associations may involve one or more amino acid residues contained in the heterologous polypeptide sequence in a fusion protein. In one example, covalent associations are between the heterologous sequence contained in a fusion protein of the invention (see, e.g., US Patent Number 5,478,925). In a specific example, the covalent associations are between the heterologous sequence contained in a Fc fusion protein of the invention (as described herein). In another specific example, covalent associations of fusion proteins of the invention are between heterologous polypeptide sequence from another protein that is capable of forming covalently associated multimers, such as for example, osteoprotegerin (see, e.g., International Publication NO: WO 98/49305, the contents of which are herein incorporated by reference in its entirety). In another embodiment, two or more polypeptides of the invention are joined through peptide linkers. Examples include those peptide linkers described in U.S. Pat. No. 5,073,627 (hereby incorporated by reference). Proteins comprising multiple polypeptides of the invention separated by peptide linkers may be produced using conventional recombinant DNA technology.

[286] Another method for preparing multimer polypeptides of the invention involves use of polypeptides of the invention fused to a leucine zipper or isoleucine zipper polypeptide sequence. Leucine zipper and isoleucine zipper domains are polypeptides that promote multimerization of the proteins in which they are found. Leucine zippers were originally identified in several DNA-binding proteins (Landschulz et al., Science 240:1759, (1988)), and have since been found in a variety of different proteins. Among the known leucine zippers are naturally occurring peptides and derivatives thereof that dimerize or trimerize. Examples of leucine zipper domains suitable for producing soluble multimeric

proteins of the invention are those described in PCT application WO 94/10308, hereby incorporated by reference. Recombinant fusion proteins comprising a polypeptide of the invention fused to a polypeptide sequence that dimerizes or trimerizes in solution are expressed in suitable host cells, and the resulting soluble multimeric fusion protein is recovered from the culture supernatant using techniques known in the art.

[287] Trimeric polypeptides of the invention may offer the advantage of enhanced biological activity. Preferred leucine zipper moieties and isoleucine moieties are those that preferentially form trimers. One example is a leucine zipper derived from lung surfactant protein D (SPD), as described in Hoppe et al. (FEBS Letters 344:191, (1994)) and in U.S. patent application Ser. No. 08/446,922, hereby incorporated by reference. Other peptides derived from naturally occurring trimeric proteins may be employed in preparing trimeric polypeptides of the invention.

[288] In another example, proteins of the invention are associated by interactions between Flag® polypeptide sequence contained in fusion proteins of the invention containing Flag® polypeptide sequence. In a further embodiment, proteins of the invention are associated by interactions between heterologous polypeptide sequence contained in Flag® fusion proteins of the invention and anti-Flag® antibody.

[289] The multimers of the invention may be generated using chemical techniques known in the art. For example, polypeptides desired to be contained in the multimers of the invention may be chemically cross-linked using linker molecules and linker molecule length optimization techniques known in the art (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety). Additionally, multimers of the invention may be generated using techniques known in the art to form one or more intermolecule cross-links between the cysteine residues located within the sequence of the polypeptides desired to be contained in the multimer (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety). Further, polypeptides of the invention may be routinely modified by the addition of cysteine or biotin to the Cterminus or N-terminus of the polypeptide and techniques known in the art may be applied to generate multimers containing one or more of these modified polypeptides (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety). Additionally, techniques known in the art may be applied to generate liposomes containing the polypeptide components desired to be contained in the multimer of the invention (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety).

[290] Alternatively, multimers of the invention may be generated using genetic engineering techniques known in the art. In one embodiment, polypeptides contained in multimers of the invention are produced recombinantly using fusion protein technology described herein or otherwise known in the art (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety). In a specific embodiment, polynucleotides coding for a homodimer of the invention are generated by ligating a polynucleotide sequence encoding a polypeptide of the invention to a sequence encoding a linker polypeptide and then further to a synthetic polynucleotide encoding the translated product of the polypeptide in the reverse orientation from the original C-terminus to the Nterminus (lacking the leader sequence) (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety). In another embodiment, recombinant techniques described herein or otherwise known in the art are applied to generate recombinant polypeptides of the invention which contain a transmembrane domain (or hydrophobic or signal peptide) and which can be incorporated by membrane reconstitution techniques into liposomes (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety).

Antibodies

[291] Further polypeptides of the invention relate to antibodies and T-cell antigen receptors (TCR) which immunospecifically bind a polypeptide, polypeptide fragment, or variant of the invention (e.g., a polypeptide or fragment or variant of the amino acid sequence of SEQ ID NO:Y or a polypeptide encoded by the cDNA contained in Clone ID No:Z, and/or an epitope, of the present invention) as determined by immunoassays well known in the art for assaying specific antibody-antigen binding. Antibodies of the invention include, but are not limited to, polyclonal, monoclonal, multispecific, human, humanized or chimeric antibodies, single chain antibodies, Fab fragments, F(ab') fragments, fragments produced by a Fab expression library, anti-idiotypic (anti-Id) antibodies (including, e.g., anti-Id antibodies to antibodies of the invention), intracellularlymade antibodies (i.e., intrabodies), and epitope-binding fragments of any of the above. The term "antibody," as used herein, refers to immunoglobulin molecules and immunologically active portions of immunoglobulin molecules, i.e., molecules that contain an antigen binding site that immunospecifically binds an antigen. The immunoglobulin molecules of the invention can be of any type (e.g., IgG, IgE, IgM, IgD, IgA and IgY), class (e.g., IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2) or subclass of immunoglobulin molecule. In preferred embodiments, the immunoglobulin molecules of the invention are IgG1. In other preferred embodiments, the immunoglobulin molecules of the invention are IgG4.

[292] Most preferably the antibodies are human antigen-binding antibody fragments of the present invention and include, but are not limited to, Fab, Fab' and F(ab')2, Fd, singlechain Fvs (scFv), single-chain antibodies, disulfide-linked Fvs (sdFv) and fragments comprising either a VL or VH domain. Antigen-binding antibody fragments, including single-chain antibodies, may comprise the variable region(s) alone or in combination with the entirety or a portion of the following: hinge region, CH1, CH2, and CH3 domains. Also included in the invention are antigen-binding fragments also comprising any combination of variable region(s) with a hinge region, CH1, CH2, and CH3 domains. The antibodies of the invention may be from any animal origin including birds and mammals. Preferably, the antibodies are human, murine (e.g., mouse and rat), donkey, ship rabbit, goat, guinea pig, camel, horse, or chicken. As used herein, "human" antibodies include antibodies having the amino acid sequence of a human immunoglobulin and include antibodies isolated from human immunoglobulin libraries or from animals transgenic for one or more human immunoglobulin and that do not express endogenous immunoglobulins, as described infra and, for example in, U.S. Patent No. 5,939,598 by Kucherlapati et al.

[293] The antibodies of the present invention may be monospecific, bispecific, trispecific or of greater multispecificity. Multispecific antibodies may be specific for different epitopes of a polypeptide of the present invention or may be specific for both a polypeptide of the present invention as well as for a heterologous epitope, such as a heterologous polypeptide or solid support material. See, e.g., PCT publications WO 93/17715; WO 92/08802; WO 91/00360; WO 92/05793; Tutt, et al., J. Immunol. 147:60-69 (1991); U.S. Patent Nos. 4,474,893; 4,714,681; 4,925,648; 5,573,920; 5,601,819; Kostelny et al., J. Immunol. 148:1547-1553 (1992).

[294] Antibodies of the present invention may be described or specified in terms of the epitope(s) or portion(s) of a polypeptide of the present invention which they recognize or specifically bind. The epitope(s) or polypeptide portion(s) may be specified as described herein, e.g., by N-terminal and C-terminal positions, or by size in contiguous amino acid residues, or listed in the Tables and Figures. Preferred epitopes of the invention include the

predicted epitopes shown in column 7 of Table 1B, as well as polynucleotides that encode these epitopes. Antibodies which specifically bind any epitope or polypeptide of the present invention may also be excluded. Therefore, the present invention includes antibodies that specifically bind polypeptides of the present invention, and allows for the exclusion of the same.

[295] Antibodies of the present invention may also be described or specified in terms of their cross-reactivity. Antibodies that do not bind any other analog, ortholog, or homolog of a polypeptide of the present invention are included. Antibodies that bind polypeptides with at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 65%, at least 60%, at least 55%, and at least 50% identity (as calculated using methods known in the art and described herein) to a polypeptide of the present invention are also included in the present invention. In specific embodiments, antibodies of the present invention cross-react with murine, rat and/or rabbit homologs of human proteins and the corresponding epitopes thereof. Antibodies that do not bind polypeptides with less than 95%, less than 90%, less than 85%, less than 80%, less than 75%, less than 70%, less than 65%, less than 60%, less than 55%, and less than 50% identity (as calculated using methods known in the art and described herein) to a polypeptide of the present invention are also included in the present invention. In a specific embodiment, the above-described cross-reactivity is with respect to any single specific antigenic or immunogenic polypeptide, or combination(s) of 2, 3, 4, 5, or more of the specific antigenic and/or immunogenic polypeptides disclosed herein. Further included in the present invention are antibodies which bind polypeptides encoded by polynucleotides which hybridize to a polynucleotide of the present invention under stringent hybridization conditions (as described herein). Antibodies of the present invention may also be described or specified in terms of their binding affinity to a polypeptide of the invention. Preferred binding affinities include those with a dissociation constant or Kd less than 5 X 10⁻² M, 10⁻² M, 5 X 10⁻³ M, 10⁻³ M, 5 X 10⁻³ 4 M, 10^{-4} M, 5×10^{-5} M, 10^{-5} M, 5×10^{-6} M, 10^{-6} M, 5×10^{-7} M, 10^{7} M, 5×10^{-8} M, 10^{-8} M, $5 \times 10^{-9} M$, $10^{-9} M$, $5 \times 10^{-10} M$, $10^{-10} M$, $5 \times 10^{-11} M$, $10^{-11} M$, $5 \times 10^{-12} M$, $10^{-12} M$, $5 \times 10^{-12} M$ 10^{-13} M, 10^{-13} M, 5 X 10^{-14} M, 10^{-14} M, 5 X 10^{-15} M, or 10^{-15} M.

[296] The invention also provides antibodies that competitively inhibit binding of an antibody to an epitope of the invention as determined by any method known in the art for determining competitive binding, for example, the immunoassays described herein. In preferred embodiments, the antibody competitively inhibits binding to the epitope by at

least 95%, at least 90%, at least 85 %, at least 80%, at least 75%, at least 70%, at least 60%, or at least 50%.

[297] Antibodies of the present invention may act as agonists or antagonists of the polypeptides of the present invention. For example, the present invention includes antibodies which disrupt the receptor/ligand interactions with the polypeptides of the invention either partially or fully. Preferably, antibodies of the present invention bind an antigenic epitope disclosed herein, or a portion thereof. The invention features both receptor-specific antibodies and ligand-specific antibodies. The invention also features receptor-specific antibodies which do not prevent ligand binding but prevent receptor activation. Receptor activation (i.e., signaling) may be determined by techniques described herein or otherwise known in the art. For example, receptor activation can be determined by detecting the phosphorylation (e.g., tyrosine or serine/threonine) of the receptor or its substrate by immunoprecipitation followed by western blot analysis (for example, as described *supra*). In specific embodiments, antibodies are provided that inhibit ligand activity or receptor activity by at least 95%, at least 85%, at least 80%, at least 75%, at least 70%, at least 60%, or at least 50% of the activity in absence of the antibody.

[298] The invention also features receptor-specific antibodies which both prevent ligand binding and receptor activation as well as antibodies that recognize the receptorligand complex, and, preferably, do not specifically recognize the unbound receptor or the unbound ligand. Likewise, included in the invention are neutralizing antibodies which bind the ligand and prevent binding of the ligand to the receptor, as well as antibodies which bind the ligand, thereby preventing receptor activation, but do not prevent the ligand from binding the receptor. Further included in the invention are antibodies which activate the receptor. These antibodies may act as receptor agonists, i.e., potentiate or activate either all or a subset of the biological activities of the ligand-mediated receptor activation, for example, by inducing dimerization of the receptor. The antibodies may be specified as agonists, antagonists or inverse agonists for biological activities comprising the specific biological activities of the peptides of the invention disclosed herein. The above antibody agonists can be made using methods known in the art. See, e.g., PCT publication WO 96/40281; U.S. Patent No. 5,811,097; Deng et al., Blood 92(6):1981-1988 (1998); Chen et al., Cancer Res. 58(16):3668-3678 (1998); Harrop et al., J. Immunol. 161(4):1786-1794 (1998); Zhu et al., Cancer Res. 58(15):3209-3214 (1998); Yoon et al., J. Immunol. 160(7):3170-3179 (1998); Prat et al., J. Cell. Sci. 111(Pt2):237-247 (1998); Pitard et al., J.

Immunol. Methods 205(2):177-190 (1997); Liautard et al., Cytokine 9(4):233-241 (1997); Carlson et al., J. Biol. Chem. 272(17):11295-11301 (1997); Taryman et al., Neuron 14(4):755-762 (1995); Muller et al., Structure 6(9):1153-1167 (1998); Bartunek et al., Cytokine 8(1):14-20 (1996) (which are all incorporated by reference herein in their entireties).

[299] Antibodies of the present invention may be used, for example, to purify, detect, and target the polypeptides of the present invention, including both *in vitro* and *in vivo* diagnostic and therapeutic methods. For example, the antibodies have utility in immunoassays for qualitatively and quantitatively measuring levels of the polypeptides of the present invention in biological samples. See, e.g., Harlow et al., Antibodies: A Laboratory Manual, (Cold Spring Harbor Laboratory Press, 2nd ed. 1988); incorporated by reference herein in its entirety.

[300] As discussed in more detail below, the antibodies of the present invention may be used either alone or in combination with other compositions. The antibodies may further be recombinantly fused to a heterologous polypeptide at the N- or C-terminus or chemically conjugated (including covalent and non-covalent conjugations) to polypeptides or other compositions. For example, antibodies of the present invention may be recombinantly fused or conjugated to molecules useful as labels in detection assays and effector molecules such as heterologous polypeptides, drugs, radionuclides, or toxins. See, e.g., PCT publications WO 92/08495; WO 91/14438; WO 89/12624; U.S. Patent No. 5,314,995; and EP 396,387; the disclosures of which are incorporated herein by reference in their entireties.

[301] The antibodies of the invention include derivatives that are modified, i.e, by the covalent attachment of any type of molecule to the antibody such that covalent attachment does not prevent the antibody from generating an anti-idiotypic response. For example, but not by way of limitation, the antibody derivatives include antibodies that have been modified, e.g., by glycosylation, acetylation, pegylation, phosphylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to a cellular ligand or other protein, etc. Any of numerous chemical modifications may be carried out by known techniques, including, but not limited to specific chemical cleavage, acetylation, formylation, metabolic synthesis of tunicamycin, etc. Additionally, the derivative may contain one or more non-classical amino acids.

[302] The antibodies of the present invention may be generated by any suitable method known in the art. Polyclonal antibodies to an antigen-of- interest can be produced by

various procedures well known in the art. For example, a polypeptide of the invention can be administered to various host animals including, but not limited to, rabbits, mice, rats, etc. to induce the production of sera containing polyclonal antibodies specific for the antigen. Various adjuvants may be used to increase the immunological response, depending on the host species, and include but are not limited to, Freund's (complete and incomplete), mineral gels such as aluminum hydroxide, surface active substances such as lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, keyhole limpet hemocyanins, dinitrophenol, and potentially useful human adjuvants such as BCG (bacille Calmette-Guerin) and corynebacterium parvum. Such adjuvants are also well known in the art.

[303] Monoclonal antibodies can be prepared using a wide variety of techniques known in the art including the use of hybridoma, recombinant, and phage display technologies, or a combination thereof. For example, monoclonal antibodies can be produced using hybridoma techniques including those known in the art and taught, for example, in Harlow et al., Antibodies: A Laboratory Manual, (Cold Spring Harbor Laboratory Press, 2nd ed. 1988); Hammerling, et al., in: Monoclonal Antibodies and T-Cell Hybridomas 563-681 (Elsevier, N.Y., 1981) (said references incorporated by reference in their entireties). The term "monoclonal antibody" as used herein is not limited to antibodies produced through hybridoma technology. The term "monoclonal antibody" refers to an antibody that is derived from a single clone, including any eukaryotic, prokaryotic, or phage clone, and not the method by which it is produced.

[304] Methods for producing and screening for specific antibodies using hybridoma technology are routine and well known in the art and are discussed in detail in the Examples. In a non-limiting example, mice can be immunized with a polypeptide of the invention or a cell expressing such peptide. Once an immune response is detected, e.g., antibodies specific for the antigen are detected in the mouse serum, the mouse spleen is harvested and splenocytes isolated. The splenocytes are then fused by well known techniques to any suitable myeloma cells, for example cells from cell line SP20 available from the ATCC. Hybridomas are selected and cloned by limited dilution. The hybridoma clones are then assayed by methods known in the art for cells that secrete antibodies capable of binding a polypeptide of the invention. Ascites fluid, which generally contains high levels of antibodies, can be generated by immunizing mice with positive hybridoma clones.

[305] Accordingly, the present invention provides methods of generating monoclonal antibodies as well as antibodies produced by the method comprising culturing a hybridoma cell secreting an antibody of the invention wherein, preferably, the hybridoma is generated by fusing splenocytes isolated from a mouse immunized with an antigen of the invention with myeloma cells and then screening the hybridomas resulting from the fusion for hybridoma clones that secrete an antibody able to bind a polypeptide of the invention.

Another well known method for producing both polyclonal and monoclonal human B cell lines is transformation using Epstein Barr Virus (EBV). Protocols for generating EBV-transformed B cell lines are commonly known in the art, such as, for example, the protocol outlined in Chapter 7.22 of Current Protocols in Immunology, Coligan et al., Eds., 1994, John Wiley & Sons, NY, which is hereby incorporated in its entirety by reference. The source of B cells for transformation is commonly human peripheral blood, but B cells for transformation may also be derived from other sources including, but not limited to, lymph nodes, tonsil, spleen, tumor tissue, and infected tissues. Tissues are generally made into single cell suspensions prior to EBV transformation. Additionally, steps may be taken to either physically remove or inactivate T cells (e.g., by treatment with cyclosporin A) in B cell-containing samples, because T cells from individuals seropositive for anti-EBV antibodies can suppress B cell immortalization by EBV.

[307] In general, the sample containing human B cells is innoculated with EBV, and cultured for 3-4 weeks. A typical source of EBV is the culture supernatant of the B95-8 cell line (ATCC #VR-1492). Physical signs of EBV transformation can generally be seen towards the end of the 3-4 week culture period. By phase-contrast microscopy, transformed cells may appear large, clear, hairy and tend to aggregate in tight clusters of cells. Initially, EBV lines are generally polyclonal. However, over prolonged periods of cell cultures, EBV lines may become monoclonal or polyclonal as a result of the selective outgrowth of particular B cell clones. Alternatively, polyclonal EBV transformed lines may be subcloned (e.g., by limiting dilution culture) or fused with a suitable fusion partner and plated at limiting dilution to obtain monoclonal B cell lines. Suitable fusion partners for EBV transformed cell lines include mouse myeloma cell lines (e.g., SP2/0, X63-Ag8.653), heteromyeloma cell lines (human x mouse; e.g, SPAM-8, SBC-H20, and CB-F7), and human cell lines (e.g., GM 1500, SKO-007, RPMI 8226, and KR-4). Thus, the present invention also provides a method of generating polyclonal or monoclonal human antibodies

against polypeptides of the invention or fragments thereof, comprising EBV-transformation of human B cells.

[308] Antibody fragments which recognize specific epitopes may be generated by known techniques. For example, Fab and F(ab')2 fragments of the invention may be produced by proteolytic cleavage of immunoglobulin molecules, using enzymes such as papain (to produce Fab fragments) or pepsin (to produce F(ab')2 fragments). F(ab')2 fragments contain the variable region, the light chain constant region and the CH1 domain of the heavy chain.

For example, the antibodies of the present invention can also be generated using [309] various phage display methods known in the art. In phage display methods, functional antibody domains are displayed on the surface of phage particles which carry the polynucleotide sequences encoding them. In a particular embodiment, such phage can be utilized to display antigen binding domains expressed from a repertoire or combinatorial antibody library (e.g., human or murine). Phage expressing an antigen binding domain that binds the antigen of interest can be selected or identified with antigen, e.g., using labeled antigen or antigen bound or captured to a solid surface or bead. Phage used in these methods are typically filamentous phage including fd and M13 binding domains expressed from phage with Fab, Fv or disulfide stabilized Fv antibody domains recombinantly fused to either the phage gene III or gene VIII protein. Examples of phage display methods that can be used to make the antibodies of the present invention include those disclosed in Brinkman et al., J. Immunol. Methods 182:41-50 (1995); Ames et al., J. Immunol. Methods 184:177-186 (1995); Kettleborough et al., Eur. J. Immunol. 24:952-958 (1994); Persic et al., Gene 187 9-18 (1997); Burton et al., Advances in Immunology 57:191-280 (1994); PCT application No. PCT/GB91/01134; PCT publications WO 90/02809; WO 91/10737; WO 92/01047; WO 92/18619; WO 93/11236; WO 95/15982; WO 95/20401; and U.S. Patent Nos. 5,698,426; 5,223,409; 5,403,484; 5,580,717; 5,427,908; 5,750,753; 5,821,047; 5,571,698; 5,427,908; 5,516,637; 5,780,225; 5,658,727; 5,733,743 and 5,969,108; each of which is incorporated herein by reference in its entirety.

[310] As described in the above references, after phage selection, the antibody coding regions from the phage can be isolated and used to generate whole antibodies, including human antibodies, or any other desired antigen binding fragment, and expressed in any desired host, including mammalian cells, insect cells, plant cells, yeast, and bacteria, e.g., as described in detail below. For example, techniques to recombinantly produce Fab, Fab' and

F(ab')2 fragments can also be employed using methods known in the art such as those disclosed in PCT publication WO 92/22324; Mullinax et al., BioTechniques 12(6):864-869 (1992); and Sawai et al., AJRI 34:26-34 (1995); and Better et al., Science 240:1041-1043 (1988) (said references incorporated by reference in their entireties).

Examples of techniques which can be used to produce single-chain Fvs and [311] antibodies include those described in U.S. Patents 4,946,778 and 5,258,498; Huston et al., Methods in Enzymology 203:46-88 (1991); Shu et al., PNAS 90:7995-7999 (1993); and Skerra et al., Science 240:1038-1040 (1988). For some uses, including in vivo use of antibodies in humans and in vitro detection assays, it may be preferable to use chimeric, humanized, or human antibodies. A chimeric antibody is a molecule in which different portions of the antibody are derived from different animal species, such as antibodies having a variable region derived from a murine monoclonal antibody and a human immunoglobulin constant region. Methods for producing chimeric antibodies are known in the art. See e.g., Morrison, Science 229:1202 (1985); Oi et al., BioTechniques 4:214 (1986); Gillies et al., (1989) J. Immunol. Methods 125:191-202; U.S. Patent Nos. 5,807,715; 4,816,567; and 4,816397, which are incorporated herein by reference in their entirety. Humanized antibodies are antibody molecules from non-human species antibody that binds the desired antigen having one or more complementarity determining regions (CDRs) from the non-human species and a framework regions from a human immunoglobulin molecule. Often, framework residues in the human framework regions will be substituted with the corresponding residue from the CDR donor antibody to alter, preferably improve, antigen binding. These framework substitutions are identified by methods well known in the art, e.g., by modeling of the interactions of the CDR and framework residues to identify framework residues important for antigen binding and sequence comparison to identify unusual framework residues at particular positions. (See, e.g., Queen et al., U.S. Patent No. 5,585,089; Riechmann et al., Nature 332:323 (1988), which are incorporated herein by reference in their entireties.) Antibodies can be humanized using a variety of techniques known in the art including, for example, CDRgrafting (EP 239,400; PCT publication WO 91/09967; U.S. Patent Nos. 5,225,539; 5,530,101; and 5,585,089), veneering or resurfacing (EP 592,106; EP 519,596; Padlan, Molecular Immunology 28(4/5):489-498 (1991); Studnicka et al., Protein Engineering 7(6):805-814 (1994); Roguska. et al., PNAS 91:969-973 (1994)), and chain shuffling (U.S. Patent No. 5,565,332).

[312] Completely human antibodies are particularly desirable for therapeutic treatment of human patients. Human antibodies can be made by a variety of methods known in the art including phage display methods described above using antibody libraries derived from human immunoglobulin sequences. See also, U.S. Patent Nos. 4,444,887 and 4,716,111; and PCT publications WO 98/46645, WO 98/50433, WO 98/24893, WO 98/16654, WO 96/34096, WO 96/33735, and WO 91/10741; each of which is incorporated herein by reference in its entirety.

Human antibodies can also be produced using transgenic mice which are [313] incapable of expressing functional endogenous immunoglobulins, but which can express For example, the human heavy and light chain human immunoglobulin genes. introduced randomly or by homologous immunoglobulin gene complexes may be recombination into mouse embryonic stem cells. Alternatively, the human variable region, constant region, and diversity region may be introduced into mouse embryonic stem cells in addition to the human heavy and light chain genes. The mouse heavy and light chain immunoglobulin genes may be rendered non-functional separately or simultaneously with the introduction of human immunoglobulin loci by homologous recombination. particular, homozygous deletion of the JH region prevents endogenous antibody production. The modified embryonic stem cells are expanded and microinjected into blastocysts to produce chimeric mice. The chimeric mice are then bred to produce homozygous offspring which express human antibodies. The transgenic mice are immunized in the normal fashion with a selected antigen, e.g., all or a portion of a polypeptide of the invention. Monoclonal antibodies directed against the antigen can be obtained from the immunized, transgenic mice using conventional hybridoma technology. The human immunoglobulin transgenes harbored by the transgenic mice rearrange during B cell differentiation, and subsequently undergo class switching and somatic mutation. Thus, using such a technique, it is possible to produce therapeutically useful IgG, IgA, IgM and IgE antibodies. For an overview of this technology for producing human antibodies, see Lonberg and Huszar, Int. Rev. Immunol. 13:65-93 (1995). For a detailed discussion of this technology for producing human antibodies and human monoclonal antibodies and protocols for producing such antibodies, see, e.g., PCT publications WO 98/24893; WO 92/01047; WO 96/34096; WO 96/33735; European Patent No. 0 598 877; U.S. Patent Nos. 5,413,923; 5,625,126; $5,633,425;\ 5,569,825;\ 5,661,016;\ \ 5,545,806;\ 5,814,318;\ 5,885,793;\ 5,916,771;\ 5,939,598;$ 6,075,181; and 6,114,598, which are incorporated by reference herein in their entirety. In addition, companies such as Abgenix, Inc. (Freemont, CA) and Genpharm (San Jose, CA) can be engaged to provide human antibodies directed against a selected antigen using technology similar to that described above.

[314] Completely human antibodies which recognize a selected epitope can be generated using a technique referred to as "guided selection." In this approach a selected non-human monoclonal antibody, e.g., a mouse antibody, is used to guide the selection of a completely human antibody recognizing the same epitope. (Jespers et al., Bio/technology 12:899-903 (1988)).

Further, antibodies to the polypeptides of the invention can, in turn, be utilized to [315] generate anti-idiotype antibodies that "mimic" polypeptides of the invention using techniques well known to those skilled in the art. (See, e.g., Greenspan & Bona, FASEB J. 7(5):437-444; (1989) and Nissinoff, J. Immunol. 147(8):2429-2438 (1991)). For example, antibodies which bind to and competitively inhibit polypeptide multimerization and/or binding of a polypeptide of the invention to a ligand can be used to generate anti-idiotypes that "mimic" the polypeptide multimerization and/or binding domain and, consequence, bind to and neutralize polypeptide and/or its ligand. Such neutralizing antiidiotypes or Fab fragments of such anti-idiotypes can be used in therapeutic regimens to neutralize polypeptide ligand(s)/receptor(s). For example, such anti-idiotypic antibodies can be used to bind a polypeptide of the invention and/or to bind its ligand(s)/receptor(s), and thereby block its biological activity. Alternatively, antibodies which bind to and enhance polypeptide multimerization and/or binding, and/or receptor/ligand multimerization, binding and/or signaling can be used to generate anti-idiotypes that function as agonists of a polypeptide of the invention and/or its ligand/receptor. Such agonistic anti-idiotypes or Fab fragments of such anti-idiotypes can be used in therapeutic regimens as agonists of the polypeptides of the invention or its ligand(s)/receptor(s). For example, such anti-idiotypic antibodies can be used to bind a polypeptide of the invention and/or to bind its ligand(s)/receptor(s), and thereby promote or enhance its biological activity.

[316] Intrabodies of the invention can be produced using methods known in the art, such as those disclosed and reviewed in Chen et al., Hum. Gene Ther. 5:595-601 (1994); Marasco, W.A., Gene Ther. 4:11-15 (1997); Rondon and Marasco, Annu. Rev. Microbiol. 51:257-283 (1997); Proba et al., J. Mol. Biol. 275:245-253 (1998); Cohen et al., Oncogene 17:2445-2456 (1998); Ohage and Steipe, J. Mol. Biol. 291:1119-1128 (1999); Ohage et al.,

J. Mol. Biol. 291:1129-1134 (1999); Wirtz and Steipe, Protein Sci. 8:2245-2250 (1999);Zhu et al., J. Immunol. Methods 231:207-222 (1999); and references cited therein.

Polynucleotides Encoding Antibodies

[317] The invention further provides polynucleotides comprising a nucleotide sequence encoding an antibody of the invention and fragments thereof. The invention also encompasses polynucleotides that hybridize under stringent or alternatively, under lower stringency hybridization conditions, e.g., as defined *supra*, to polynucleotides that encode an antibody, preferably, that specifically binds to a polypeptide of the invention, preferably, an antibody that binds to a polypeptide having the amino acid sequence of SEQ ID NO:Y, to a polypeptide encoded by a portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2, and/or to a polypeptide encoded by the cDNA contained in Clone ID NO:Z.

[318] The polynucleotides may be obtained, and the nucleotide sequence of the polynucleotides determined, by any method known in the art. For example, if the nucleotide sequence of the antibody is known, a polynucleotide encoding the antibody may be assembled from chemically synthesized oligonucleotides (e.g., as described in Kutmeier et al., BioTechniques 17:242 (1994)), which, briefly, involves the synthesis of overlapping oligonucleotides containing portions of the sequence encoding the antibody, annealing and ligating of those oligonucleotides, and then amplification of the ligated oligonucleotides by PCR.

Alternatively, a polynucleotide encoding an antibody may be generated from nucleic acid from a suitable source. If a clone containing a nucleic acid encoding a particular antibody is not available, but the sequence of the antibody molecule is known, a nucleic acid encoding the immunoglobulin may be chemically synthesized or obtained from a suitable source (e.g., an antibody cDNA library, or a cDNA library generated from, or nucleic acid, preferably poly A+ RNA, isolated from, any tissue or cells expressing the antibody, such as hybridoma cells selected to express an antibody of the invention) by PCR amplification using synthetic primers hybridizable to the 3' and 5' ends of the sequence or by cloning using an oligonucleotide probe specific for the particular gene sequence to identify, e.g., a cDNA clone from a cDNA library that encodes the antibody. Amplified nucleic acids generated by PCR may then be cloned into replicable cloning vectors using any method well known in the art.

Once the nucleotide sequence and corresponding amino acid sequence of the antibody is determined, the nucleotide sequence of the antibody may be manipulated using methods well known in the art for the manipulation of nucleotide sequences, e.g., recombinant DNA techniques, site directed mutagenesis, PCR, etc. (see, for example, the techniques described in Sambrook et al., 1990, Molecular Cloning, A Laboratory Manual, 2d Ed., Cold Spring Harbor Laboratory, Cold Spring Harbor, NY and Ausubel et al., eds., 1998, Current Protocols in Molecular Biology, John Wiley & Sons, NY, which are both incorporated by reference herein in their entireties), to generate antibodies having a different amino acid sequence, for example to create amino acid substitutions, deletions, and/or insertions.

In a specific embodiment, the amino acid sequence of the heavy and/or light [321] chain variable domains may be inspected to identify the sequences of the complementarity determining regions (CDRs) by methods that are well know in the art, e.g., by comparison to known amino acid sequences of other heavy and light chain variable regions to determine the regions of sequence hypervariability. Using routine recombinant DNA techniques, one or more of the CDRs may be inserted within framework regions, e.g., into human framework regions to humanize a non-human antibody, as described supra. The framework regions may be naturally occurring or consensus framework regions, and preferably human framework regions (see, e.g., Chothia et al., J. Mol. Biol. 278: 457-479 (1998) for a listing of human framework regions). Preferably, the polynucleotide generated by the combination of the framework regions and CDRs encodes an antibody that specifically binds a Preferably, as discussed supra, one or more amino acid polypeptide of the invention. substitutions may be made within the framework regions, and, preferably, the amino acid substitutions improve binding of the antibody to its antigen. Additionally, such methods may be used to make amino acid substitutions or deletions of one or more variable region cysteine residues participating in an intrachain disulfide bond to generate antibody molecules lacking one or more intrachain disulfide bonds. Other alterations to the polynucleotide are encompassed by the present invention and within the skill of the art.

[322] In addition, techniques developed for the production of "chimeric antibodies" (Morrison et al., Proc. Natl. Acad. Sci. 81:851-855 (1984); Neuberger et al., Nature 312:604-608 (1984); Takeda et al., Nature 314:452-454 (1985)) by splicing genes from a mouse antibody molecule of appropriate antigen specificity together with genes from a human antibody molecule of appropriate biological activity can be used. As described

supra, a chimeric antibody is a molecule in which different portions are derived from different animal species, such as those having a variable region derived from a murine mAb and a human immunoglobulin constant region, e.g., humanized antibodies.

[323] Alternatively, techniques described for the production of single chain antibodies (U.S. Patent No. 4,946,778; Bird, Science 242:423- 42 (1988); Huston et al., Proc. Natl. Acad. Sci. USA 85:5879-5883 (1988); and Ward et al., Nature 334:544-54 (1989)) can be adapted to produce single chain antibodies. Single chain antibodies are formed by linking the heavy and light chain fragments of the Fv region via an amino acid bridge, resulting in a single chain polypeptide. Techniques for the assembly of functional Fv fragments in E. coli may also be used (Skerra et al., Science 242:1038- 1041 (1988)).

Methods of Producing Antibodies

[324] The antibodies of the invention can be produced by any method known in the art for the synthesis of antibodies, in particular, by chemical synthesis or preferably, by recombinant expression techniques. Methods of producing antibodies include, but are not limited to, hybridoma technology, EBV transformation, and other methods discussed herein as well as through the use recombinant DNA technology, as discussed below.

Recombinant expression of an antibody of the invention, or fragment, derivative [325] or analog thereof, (e.g., a heavy or light chain of an antibody of the invention or a single chain antibody of the invention), requires construction of an expression vector containing a polynucleotide that encodes the antibody. Once a polynucleotide encoding an antibody molecule or a heavy or light chain of an antibody, or portion thereof (preferably containing the heavy or light chain variable domain), of the invention has been obtained, the vector for the production of the antibody molecule may be produced by recombinant DNA technology using techniques well known in the art. Thus, methods for preparing a protein by expressing a polynucleotide containing an antibody encoding nucleotide sequence are described herein. Methods which are well known to those skilled in the art can be used to construct expression vectors containing antibody coding sequences and appropriate transcriptional and translational control signals. These methods include, for example, in vitro recombinant DNA techniques, synthetic techniques, and in vivo genetic recombination. The invention, thus, provides replicable vectors comprising a nucleotide sequence encoding an antibody molecule of the invention, or a heavy or light chain thereof, or a heavy or light chain variable domain, operably linked to a promoter. Such vectors may include the nucleotide sequence encoding the constant region of the antibody molecule (see, e.g., PCT Publication WO 86/05807; PCT Publication WO 89/01036; and U.S. Patent No. 5,122,464) and the variable domain of the antibody may be cloned into such a vector for expression of the entire heavy or light chain.

[326] The expression vector is transferred to a host cell by conventional techniques and the transfected cells are then cultured by conventional techniques to produce an antibody of the invention. Thus, the invention includes host cells containing a polynucleotide encoding an antibody of the invention, or a heavy or light chain thereof, or a single chain antibody of the invention, operably linked to a heterologous promoter. In preferred embodiments for the expression of double-chained antibodies, vectors encoding both the heavy and light chains may be co-expressed in the host cell for expression of the entire immunoglobulin molecule, as detailed below.

A variety of host-expression vector systems may be utilized to express the [327] antibody molecules of the invention. Such host-expression systems represent vehicles by which the coding sequences of interest may be produced and subsequently purified, but also represent cells which may, when transformed or transfected with the appropriate nucleotide coding sequences, express an antibody molecule of the invention in situ. These include but are not limited to microorganisms such as bacteria (e.g., E. coli, B. subtilis) transformed with recombinant bacteriophage DNA, plasmid DNA or cosmid DNA expression vectors containing antibody coding sequences; yeast (e.g., Saccharomyces, Pichia) transformed with recombinant yeast expression vectors containing antibody coding sequences; insect cell systems infected with recombinant virus expression vectors (e.g., baculovirus) containing antibody coding sequences; plant cell systems infected with recombinant virus expression vectors (e.g., cauliflower mosaic virus, CaMV; tobacco mosaic virus, TMV) or transformed with recombinant plasmid expression vectors (e.g., Ti plasmid) containing antibody coding sequences; or mammalian cell systems (e.g., COS, CHO, BHK, 293, 3T3 cells) harboring recombinant expression constructs containing promoters derived from the genome of mammalian cells (e.g., metallothionein promoter) or from mammalian viruses (e.g., the adenovirus late promoter; the vaccinia virus 7.5K promoter). Preferably, bacterial cells such as Escherichia coli, and more preferably, eukaryotic cells, especially for the expression of whole recombinant antibody molecule, are used for the expression of a recombinant antibody molecule. For example, mammalian cells such as Chinese hamster ovary cells (CHO), in conjunction with a vector such as the major intermediate early gene promoter element from human cytomegalovirus is an effective expression system for antibodies (Foecking et al., Gene 45:101 (1986); Cockett et al., Bio/Technology 8:2 (1990)).

[328] In bacterial systems, a number of expression vectors may be advantageously selected depending upon the use intended for the antibody molecule being expressed. For example, when a large quantity of such a protein is to be produced, for the generation of pharmaceutical compositions of an antibody molecule, vectors which direct the expression of high levels of fusion protein products that are readily purified may be desirable. Such vectors include, but are not limited, to the E. coli expression vector pUR278 (Ruther et al., EMBO J. 2:1791 (1983)), in which the antibody coding sequence may individually into the vector in frame with the lac Z coding region so that a fusion protein is produced; pIN vectors (Inouye & Inouye, Nucleic Acids Res. 13:3101-3109 (1985); Van Heeke & Schuster, J. Biol. Chem. 24:5503-5509 (1989)); and the like. pGEX vectors may also be used to express foreign polypeptides as fusion proteins with glutathione Stransferase (GST). In general, such fusion proteins are soluble and can easily be purified from lysed cells by adsorption and binding to matrix glutathione-agarose beads followed by elution in the presence of free glutathione. The pGEX vectors are designed to include thrombin or factor Xa protease cleavage sites so that the cloned target gene product can be released from the GST moiety.

[329] In an insect system, Autographa californica nuclear polyhedrosis virus (AcNPV) is used as a vector to express foreign genes. The virus grows in *Spodoptera frugiperda* cells. The antibody coding sequence may be cloned individually into non-essential regions (for example the polyhedrin gene) of the virus and placed under control of an AcNPV promoter (for example the polyhedrin promoter).

[330] In mammalian host cells, a number of viral-based expression systems may be utilized. In cases where an adenovirus is used as an expression vector, the antibody coding sequence of interest may be ligated to an adenovirus transcription/translation control complex, e.g., the late promoter and tripartite leader sequence. This chimeric gene may then be inserted in the adenovirus genome by in vitro or *in vivo* recombination. Insertion in a non- essential region of the viral genome (e.g., region E1 or E3) will result in a recombinant virus that is viable and capable of expressing the antibody molecule in infected hosts. (e.g., see Logan & Shenk, Proc. Natl. Acad. Sci. USA 81:355-359 (1984)). Specific initiation signals may also be required for efficient translation of inserted antibody

coding sequences. These signals include the ATG initiation codon and adjacent sequences. Furthermore, the initiation codon must be in phase with the reading frame of the desired coding sequence to ensure translation of the entire insert. These exogenous translational control signals and initiation codons can be of a variety of origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of appropriate transcription enhancer elements, transcription terminators, etc. (see Bittner et al., Methods in Enzymol. 153:51-544 (1987)).

[331] In addition, a host cell strain may be chosen which modulates the expression of the inserted sequences, or modifies and processes the gene product in the specific fashion desired. Such modifications (e.g., glycosylation) and processing (e.g., cleavage) of protein products may be important for the function of the protein. Different host cells have characteristic and specific mechanisms for the post-translational processing and modification of proteins and gene products. Appropriate cell lines or host systems can be chosen to ensure the correct modification and processing of the foreign protein expressed. To this end, eukaryotic host cells which possess the cellular machinery for proper processing of the primary transcript, glycosylation, and phosphorylation of the gene product may be used. Such mammalian host cells include but are not limited to CHO, VERY, BHK, Hela, COS, MDCK, 293, 3T3, WI38, and in particular, breast cancer cell lines such as, for example, BT483, Hs578T, HTB2, BT20 and T47D, and normal mammary gland cell line such as, for example, CRL7030 and Hs578Bst.

[332] For long-term, high-yield production of recombinant proteins, stable expression is preferred. For example, cell lines which stably express the antibody molecule may be engineered. Rather than using expression vectors which contain viral origins of replication, host cells can be transformed with DNA controlled by appropriate expression control elements (e.g., promoter, enhancer, sequences, transcription terminators, polyadenylation sites, etc.), and a selectable marker. Following the introduction of the foreign DNA, engineered cells may be allowed to grow for 1-2 days in an enriched media, and then are switched to a selective media. The selectable marker in the recombinant plasmid confers resistance to the selection and allows cells to stably integrate the plasmid into their chromosomes and grow to form foci which in turn can be cloned and expanded into cell lines. This method may advantageously be used to engineer cell lines which express the antibody molecule. Such engineered cell lines may be particularly useful in screening and evaluation of compounds that interact directly or indirectly with the antibody molecule.

A number of selection systems may be used, including but not limited to the [333] herpes simplex virus thymidine kinase (Wigler et al., Cell 11:223 (1977)), hypoxanthineguanine phosphoribosyltransferase (Szybalska & Szybalski, Proc. Natl. Acad. Sci. USA 48:202 (1992)), and adenine phosphoribosyltransferase (Lowy et al., Cell 22:817 (1980)) genes can be employed in tk-, hgprt- or aprt- cells, respectively. Also, antimetabolite resistance can be used as the basis of selection for the following genes: dhfr, which confers resistance to methotrexate (Wigler et al., Natl. Acad. Sci. USA 77:357 (1980); O'Hare et al., Proc. Natl. Acad. Sci. USA 78:1527 (1981)); gpt, which confers resistance to mycophenolic acid (Mulligan & Berg, Proc. Natl. Acad. Sci. USA 78:2072 (1981)); neo, which confers resistance to the aminoglycoside G-418 Clinical Pharmacy 12:488-505; Wu and Wu, Biotherapy 3:87-95 (1991); Tolstoshev, Ann. Rev. Pharmacol. Toxicol. 32:573-596 (1993); Mulligan, Science 260:926-932 (1993); and Morgan and Anderson, Ann. Rev. Biochem. 62:191-217 (1993); May, 1993, TIB TECH 11(5):155-215 (1993)); and hygro, which confers resistance to hygromycin (Santerre et al., Gene 30:147 (1984)). Methods commonly known in the art of recombinant DNA technology may be routinely applied to select the desired recombinant clone, and such methods are described, for example, in Ausubel et al. (eds.), Current Protocols in Molecular Biology, John Wiley & Sons, NY (1993); Kriegler, Gene Transfer and Expression, A Laboratory Manual, Stockton Press, NY (1990); and in Chapters 12 and 13, Dracopoli et al. (eds), Current Protocols in Human Genetics, John Wiley & Sons, NY (1994); Colberre-Garapin et al., J. Mol. Biol. 150:1 (1981), which are incorporated by reference herein in their entireties.

The expression levels of an antibody molecule can be increased by vector amplification (for a review, see Bebbington and Hentschel, The use of vectors based on gene amplification for the expression of cloned genes in mammalian cells in DNA cloning, Vol.3. (Academic Press, New York, 1987)). When a marker in the vector system expressing antibody is amplifiable, increase in the level of inhibitor present in culture of host cell will increase the number of copies of the marker gene. Since the amplified region is associated with the antibody gene, production of the antibody will also increase (Crouse et al., Mol. Cell. Biol. 3:257 (1983)).

[335] Vectors which use glutamine synthase (GS) or DHFR as the selectable markers can be amplified in the presence of the drugs methionine sulphoximine or methotrexate, respectively. An advantage of glutamine synthase based vectors are the availability of cell lines (e.g., the murine myeloma cell line, NS0) which are glutamine synthase negative.

Glutamine synthase expression systems can also function in glutamine synthase expressing cells (e.g. Chinese Hamster Ovary (CHO) cells) by providing additional inhibitor to prevent the functioning of the endogenous gene. A glutamine synthase expression system and components thereof are detailed in PCT publications: WO87/04462; WO86/05807; WO89/01036; WO89/10404; and WO91/06657 which are incorporated in their entireties by reference herein. Additionally, glutamine synthase expression vectors that may be used according to the present invention are commercially available from suplliers, including, for example Lonza Biologics, Inc. (Portsmouth, NH). Expression and production of monoclonal antibodies using a GS expression system in murine myeloma cells is described in Bebbington *et al.*, *Bio/technology* 10:169(1992) and in Biblia and Robinson *Biotechnol. Prog.* 11:1 (1995) which are incorporated in their entirities by reference herein.

[336] The host cell may be co-transfected with two expression vectors of the invention, the first vector encoding a heavy chain derived polypeptide and the second vector encoding a light chain derived polypeptide. The two vectors may contain identical selectable markers which enable equal expression of heavy and light chain polypeptides. Alternatively, a single vector may be used which encodes, and is capable of expressing, both heavy and light chain polypeptides. In such situations, the light chain should be placed before the heavy chain to avoid an excess of toxic free heavy chain (Proudfoot, Nature 322:52 (1986); Kohler, Proc. Natl. Acad. Sci. USA 77:2197 (1980)). The coding sequences for the heavy and light chains may comprise cDNA or genomic DNA.

Once an antibody molecule of the invention has been produced by an animal, chemically synthesized, or recombinantly expressed, it may be purified by any method known in the art for purification of an immunoglobulin molecule, for example, by chromatography (e.g., ion exchange, affinity, particularly by affinity for the specific antigen after Protein A, and sizing column chromatography), centrifugation, differential solubility, or by any other standard technique for the purification of proteins. In addition, the antibodies of the present invention or fragments thereof can be fused to heterologous polypeptide sequences described herein or otherwise known in the art, to facilitate purification.

[338] The present invention encompasses antibodies recombinantly fused or chemically conjugated (including both covalently and non-covalently conjugations) to a polypeptide (or portion thereof, preferably at least 10, 20, 30, 40, 50, 60, 70, 80, 90 or 100 amino acids of the polypeptide) of the present invention to generate fusion proteins. The fusion does

not necessarily need to be direct, but may occur through linker sequences. The antibodies may be specific for antigens other than polypeptides (or portion thereof, preferably at least 10, 20, 30, 40, 50, 60, 70, 80, 90 or 100 amino acids of the polypeptide) of the present invention. For example, antibodies may be used to target the polypeptides of the present invention to particular cell types, either in vitro or *in vivo*, by fusing or conjugating the polypeptides of the present invention to antibodies specific for particular cell surface receptors. Antibodies fused or conjugated to the polypeptides of the present invention may also be used in in vitro immunoassays and purification methods using methods known in the art. See e.g., Harbor et al., *supra*, and PCT publication WO 93/21232; EP 439,095; Naramura et al., Immunol. Lett. 39:91-99 (1994); U.S. Patent 5,474,981; Gillies et al., PNAS 89:1428-1432 (1992); Fell et al., J. Immunol. 146:2446-2452 (1991), which are incorporated by reference in their entireties.

The present invention further includes compositions comprising the polypeptides [339] of the present invention fused or conjugated to antibody domains other than the variable regions. For example, the polypeptides of the present invention may be fused or conjugated to an antibody Fc region, or portion thereof. The antibody portion fused to a polypeptide of the present invention may comprise the constant region, hinge region, CH1 domain, CH2 domain, and CH3 domain or any combination of whole domains or portions thereof. The polypeptides may also be fused or conjugated to the above antibody portions to form multimers. For example, Fc portions fused to the polypeptides of the present invention can form dimers through disulfide bonding between the Fc portions. Higher multimeric forms can be made by fusing the polypeptides to portions of IgA and IgM. Methods for fusing or conjugating the polypeptides of the present invention to antibody portions are known in the art. See, e.g., U.S. Patent Nos. 5,336,603; 5,622,929; 5,359,046; 5,349,053; 5,447,851; 5,112,946; EP 307,434; EP 367,166; PCT publications WO 96/04388; WO 91/06570; Ashkenazi et al., Proc. Natl. Acad. Sci. USA 88:10535-10539 (1991); Zheng et al., J. Immunol. 154:5590-5600 (1995); and Vil et al., Proc. Natl. Acad. Sci. USA 89:11337-11341 (1992) (said references incorporated by reference in their entireties).

[340] As discussed, *supra*, the polypeptides corresponding to a polypeptide, polypeptide fragment, or a variant of SEQ ID NO:Y may be fused or conjugated to the above antibody portions to increase the *in vivo* half life of the polypeptides or for use in immunoassays using methods known in the art. Further, the polypeptides corresponding to SEQ ID NO:Y may be fused or conjugated to the above antibody portions to facilitate

purification. One reported example describes chimeric proteins consisting of the first two domains of the human CD4-polypeptide and various domains of the constant regions of the heavy or light chains of mammalian immunoglobulins. See EP 394,827; and Traunecker et al., Nature 331:84-86 (1988). The polypeptides of the present invention fused or conjugated to an antibody having disulfide- linked dimeric structures (due to the IgG) may also be more efficient in binding and neutralizing other molecules, than the monomeric secreted protein or protein fragment alone. See, for example, Fountoulakis et al., J. Biochem. 270:3958-3964 (1995). In many cases, the Fc part in a fusion protein is beneficial in therapy and diagnosis, and thus can result in, for example, improved pharmacokinetic properties. See, for example, EP A 232,262. Alternatively, deleting the Fc part after the fusion protein has been expressed, detected, and purified, would be desired. For example, the Fc portion may hinder therapy and diagnosis if the fusion protein is used as an antigen for immunizations. In drug discovery, for example, human proteins, such as hIL-5, have been fused with Fc portions for the purpose of high-throughput screening assays to identify antagonists of hIL-5. (See, Bennett et al., J. Molecular Recognition 8:52-58 (1995); Johanson et al., J. Biol. Chem. 270:9459-9471 (1995)).

[341] Moreover, the antibodies or fragments thereof of the present invention can be fused to marker sequences, such as a peptide to facilitate purification. In preferred embodiments, the marker amino acid sequence is a hexa-histidine peptide, such as the tag provided in a pQE vector (QIAGEN, Inc., 9259 Eton Avenue, Chatsworth, CA, 91311), among others, many of which are commercially available. As described in Gentz et al., Proc. Natl. Acad. Sci. USA 86:821-824 (1989), for instance, hexa-histidine provides for convenient purification of the fusion protein. Other peptide tags useful for purification include, but are not limited to, the "HA" tag, which corresponds to an epitope derived from the influenza hemagglutinin protein (Wilson et al., Cell 37:767 (1984)) and the "flag" tag.

[342] The present invention further encompasses antibodies or fragments thereof conjugated to a diagnostic or therapeutic agent. The antibodies can be used diagnostically to, for example, monitor the development or progression of a tumor as part of a clinical testing procedure to, e.g., determine the efficacy of a given treatment regimen. Detection can be facilitated by coupling the antibody to a detectable substance. Examples of detectable substances include various enzymes, prosthetic groups, fluorescent materials, luminescent materials, bioluminescent materials, radioactive materials, positron emitting metals using various positron emission tomographies, and nonradioactive paramagnetic

metal ions. The detectable substance may be coupled or conjugated either directly to the antibody (or fragment thereof) or indirectly, through an intermediate (such as, for example, a linker known in the art) using techniques known in the art. See, for example, U.S. Patent No. 4,741,900 for metal ions which can be conjugated to antibodies for use as diagnostics according to the present invention. Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, beta-galactosidase, or acetylcholinesterase; examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes luminol; examples of bioluminescent materials include luciferase, luciferin, and aequorin; and examples of suitable radioactive material include 125I, 13II, 11IIn or 99Tc.

Further, an antibody or fragment thereof may be conjugated to a therapeutic [343] moiety such as a cytotoxin, e.g., a cytostatic or cytocidal agent, a therapeutic agent or a radioactive metal ion, e.g., alpha-emitters such as, for example, 213Bi. A cytotoxin or cytotoxic agent includes any agent that is detrimental to cells. Examples include paclitaxol, cytochalasin B, gramicidin D, ethidium bromide, emetine, mitomycin, etoposide, tenoposide, vincristine, vinblastine, colchicin, doxorubicin, daunorubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, 1-dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, and puromycin and analogs or homologs thereof. Therapeutic agents include, but are not limited to, antimetabolites (e.g., methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine), alkylating agents (e.g., mechlorethamine, thioepa chlorambucil, melphalan, carmustine (BSNU) and lomustine (CCNU), cyclothosphamide, busulfan, dibromomannitol, streptozotocin, mitomycin C, and cis- dichlorodiamine platinum (II) (DDP) cisplatin), anthracyclines (e.g., daunorubicin (formerly daunomycin) and doxorubicin), antibiotics (e.g., dactinomycin (formerly actinomycin), bleomycin, mithramycin, and anthramycin (AMC)), and anti-mitotic agents (e.g., vincristine and vinblastine).

[344] The conjugates of the invention can be used for modifying a given biological response, the therapeutic agent or drug moiety is not to be construed as limited to classical chemical therapeutic agents. For example, the drug moiety may be a protein or polypeptide possessing a desired biological activity. Such proteins may include, for example, a toxin such as abrin, ricin A, pseudomonas exotoxin, or diphtheria toxin; a protein such as tumor

necrosis factor, a-interferon, β-interferon, nerve growth factor, platelet derived growth factor, tissue plasminogen activator, an apoptotic agent, e.g., TNF-alpha, TNF-beta, AIM I (See, International Publication No. WO 97/33899), AIM II (See, International Publication No. WO 97/34911), Fas Ligand (Takahashi *et al.*, *Int. Immunol.*, 6:1567-1574 (1994)), VEGI (See, International Publication No. WO 99/23105), a thrombotic agent or an antiangiogenic agent, e.g., angiostatin or endostatin; or, biological response modifiers such as, for example, lymphokines, interleukin-1 ("IL-1"), interleukin-2 ("IL-2"), interleukin-6 ("IL-6"), granulocyte macrophage colony stimulating factor ("GM-CSF"), granulocyte colony stimulating factor ("G-CSF"), or other growth factors.

[345] Antibodies may also be attached to solid supports, which are particularly useful for immunoassays or purification of the target antigen. Such solid supports include, but are not limited to, glass, cellulose, polyacrylamide, nylon, polystyrene, polyvinyl chloride or polypropylene.

[346] Techniques for conjugating such therapeutic moiety to antibodies are well known. See, for example, Arnon et al., "Monoclonal Antibodies For Immunotargeting Of Drugs In Cancer Therapy", in Monoclonal Antibodies And Cancer Therapy, Reisfeld et al. (eds.), pp. 243-56 (Alan R. Liss, Inc. 1985); Hellstrom et al., "Antibodies For Drug Delivery", in Controlled Drug Delivery (2nd Ed.), Robinson et al. (eds.), pp. 623-53 (Marcel Dekker, Inc. 1987); Thorpe, "Antibody Carriers Of Cytotoxic Agents In Cancer Therapy: A Review", in Monoclonal Antibodies '84: Biological And Clinical Applications, Pinchera et al. (eds.), pp. 475-506 (1985); "Analysis, Results, And Future Prospective Of The Therapeutic Use Of Radiolabeled Antibody In Cancer Therapy", in Monoclonal Antibodies For Cancer Detection And Therapy, Baldwin et al. (eds.), pp. 303-16 (Academic Press 1985), and Thorpe et al., "The Preparation And Cytotoxic Properties Of Antibody-Toxin Conjugates", Immunol. Rev. 62:119-58 (1982).

[347] Alternatively, an antibody can be conjugated to a second antibody to form an antibody heteroconjugate as described by Segal in U.S. Patent No. 4,676,980, which is incorporated herein by reference in its entirety.

[348] An antibody, with or without a therapeutic moiety conjugated to it, administered alone or in combination with cytotoxic factor(s) and/or cytokine(s) can be used as a therapeutic.

Immunophenotyping

[349] The antibodies of the invention may be utilized for immunophenotyping of cell lines and biological samples. Translation products of the gene of the present invention may be useful as cell-specific markers, or more specifically as cellular markers that are differentially expressed at various stages of differentiation and/or maturation of particular cell types. Monoclonal antibodies directed against a specific epitope, or combination of epitopes, will allow for the screening of cellular populations expressing the marker. Various techniques can be utilized using monoclonal antibodies to screen for cellular populations expressing the marker(s), and include magnetic separation using antibody-coated magnetic beads, "panning" with antibody attached to a solid matrix (i.e., plate), and flow cytometry (See, e.g., U.S. Patent 5,985,660; and Morrison et al., Cell, 96:737-49 (1999)).

[350] These techniques allow for the screening of particular populations of cells, such as might be found with hematological malignancies (i.e. minimal residual disease (MRD) in acute leukemic patients) and "non-self" cells in transplantations to prevent Graft-versus-Host Disease (GVHD). Alternatively, these techniques allow for the screening of hematopoietic stem and progenitor cells capable of undergoing proliferation and/or differentiation, as might be found in human umbilical cord blood.

Assays For Antibody Binding

The antibodies of the invention may be assayed for immunospecific binding by any method known in the art. The immunoassays which can be used include but are not limited to competitive and non-competitive assay systems using techniques such as western blots, radioimmunoassays, ELISA (enzyme linked immunosorbent assay), "sandwich" immunoassays, immunoprecipitation assays, precipitin reactions, gel diffusion precipitin reactions, immunodiffusion assays, agglutination assays, complement-fixation assays, immunoradiometric assays, fluorescent immunoassays, and protein A immunoassays, to name but a few. Such assays are routine and well known in the art (see, e.g., Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York, which is incorporated by reference herein in its entirety). Exemplary immunoassays are described briefly below (but are not intended by way of limitation).

[352] Immunoprecipitation protocols generally comprise lysing a population of cells in a lysis buffer such as RIPA buffer (1% NP-40 or Triton X- 100, 1% sodium deoxycholate, 0.1% SDS, 0.15 M NaCl, 0.01 M sodium phosphate at pH 7.2, 1% Trasylol) supplemented

with protein phosphatase and/or protease inhibitors (e.g., EDTA, PMSF, aprotinin, sodium vanadate), adding the antibody of interest to the cell lysate, incubating for a period of time (e.g., 1-4 hours) at 4° C, adding protein A and/or protein G sepharose beads to the cell lysate, incubating for about an hour or more at 4° C, washing the beads in lysis buffer and resuspending the beads in SDS/sample buffer. The ability of the antibody of interest to immunoprecipitate a particular antigen can be assessed by, e.g., western blot analysis. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the binding of the antibody to an antigen and decrease the background (e.g., preclearing the cell lysate with sepharose beads). For further discussion regarding immunoprecipitation protocols see, e.g., Ausubel et al., eds., (1994), Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York, section 10.16.1.

[353] Western blot analysis generally comprises preparing protein samples, electrophoresis of the protein samples in a polyacrylamide gel (e.g., 8%- 20% SDS-PAGE depending on the molecular weight of the antigen), transferring the protein sample from the polyacrylamide gel to a membrane such as nitrocellulose, PVDF or nylon, blocking the membrane in blocking solution (e.g., PBS with 3% BSA or non-fat milk), washing the membrane in washing buffer (e.g., PBS-Tween 20), blocking the membrane with primary antibody (the antibody of interest) diluted in blocking buffer, washing the membrane in washing buffer, blocking the membrane with a secondary antibody (which recognizes the primary antibody, e.g., an anti-human antibody) conjugated to an enzymatic substrate (e.g., horseradish peroxidase or alkaline phosphatase) or radioactive molecule (e.g., 32P or 125I) diluted in blocking buffer, washing the membrane in wash buffer, and detecting the presence of the antigen. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the signal detected and to reduce the background noise. For further discussion regarding western blot protocols see, e.g., Ausubel et al, eds, (1994), Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York, section 10.8.1.

[354] ELISAs comprise preparing antigen, coating the well of a 96 well microtiter plate with the antigen, adding the antibody of interest conjugated to a detectable compound such as an enzymatic substrate (e.g., horseradish peroxidase or alkaline phosphatase) to the well and incubating for a period of time, and detecting the presence of the antigen. In ELISAs the antibody of interest does not have to be conjugated to a detectable compound; instead, a second antibody (which recognizes the antibody of interest) conjugated to a detectable

compound may be added to the well. Further, instead of coating the well with the antigen, the antibody may be coated to the well. In this case, a second antibody conjugated to a detectable compound may be added following the addition of the antigen of interest to the coated well. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the signal detected as well as other variations of ELISAs known in the art. For further discussion regarding ELISAs see, e.g., Ausubel et al, eds, (1994), Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York, section 11.2.1.

[355] The binding affinity of an antibody to an antigen and the off-rate of an antibody-antigen interaction can be determined by competitive binding assays. One example of a competitive binding assay is a radioimmunoassay comprising the incubation of labeled antigen (e.g., 3H or 125I) with the antibody of interest in the presence of increasing amounts of unlabeled antigen, and the detection of the antibody bound to the labeled antigen. The affinity of the antibody of interest for a particular antigen and the binding off-rates can be determined from the data by scatchard plot analysis. Competition with a second antibody can also be determined using radioimmunoassays. In this case, the antigen is incubated with antibody of interest conjugated to a labeled compound (e.g., 3H or 125I) in the presence of increasing amounts of an unlabeled second antibody.

[356] Antibodies of the invention may be characterized using immunocytochemisty methods on cells (e.g., mammalian cells, such as CHO cells) transfected with a vector enabling the expression of an antigen or with vector alone using techniques commonly known in the art. Antibodies that bind antigen transfected cells, but not vector-only transfected cells, are antigen specific.

Therapeutic Uses

Table 1D: In preferred embodiments, the present invention encompasses a method of treating a disease or disorder listed in the "Preferred Indications" column of Table 1D; comprising administering to a patient in which such treatment, prevention, or amelioration is desired a protein, nucleic acid, or antibody of the invention (or fragment or variant thereof) represented by Table 1A and Table 1D (in the same row as the disease or disorder to be treated is listed in the "Preferred Indications" column of Table 1D) in an amount effective to treat, prevent, or ameliorate the disease or disorder.

[358] As indicated in Table 1D, the polynucleotides, polypeptides, agonists, or antagonists of the present invention (including antibodies) can be used in assays to test for one or more biological activities. If these polynucleotides and polypeptides do exhibit activity in a particular assay, it is likely that these molecules may be involved in the diseases associated with the biological activity. Thus, the polynucleotides or polypeptides, or agonists or antagonists thereof (including antibodies) could be used to treat the associated disease.

[359] The present invention encompasses methods of preventing, treating, diagnosing, or ameliorating a disease or disorder. In preferred embodiments, the present invention encompasses a method of treating a disease or disorder listed in the "Preferred Indications" column of Table 1D; comprising administering to a patient in which such treatment, prevention, or amelioration is desired a protein, nucleic acid, or antibody of the invention (or fragment or variant thereof) in an amount effective to treat, prevent, diagnose, or ameliorate the disease or disorder. The first and second columns of Table 1D show the "Gene No." and "cDNA Clone ID No.", respectively, indicating certain nucleic acids and proteins (or antibodies against the same) of the invention (including polynucleotide, polypeptide, and antibody fragments or variants thereof) that may be used in preventing, treating, diagnosing, or ameliorating the disease(s) or disorder(s) indicated in the corresponding row in Column 3 of Table 1D.

[360] In another embodiment, the present invention also encompasses methods of preventing, treating, diagnosing, or ameliorating a disease or disorder listed in the "Preferred Indications" column of Table 1D; comprising administering to a patient combinations of the proteins, nucleic acids, or antibodies of the invention (or fragments or variants thereof), sharing similar indications as shown in the corresponding rows in Column 3 of Table 1D.

[361] The "Preferred Indication" column describes diseases, disorders, and/or conditions that may be treated, prevented, diagnosed, or ameliorated by a protein, nucleic acid, or antibody of the invention (or fragment or variant thereof).

[362] The recitation of "Cancer" in the "Preferred Indication" column indicates that the corresponding nucleic acid and protein, or antibody against the same, of the invention (or fragment or variant thereof) may be used for example, to diagnose, treat, prevent, and/or ameliorate diseases and/or disorders relating to neoplastic diseases (e.g., leukemias, cancers, and/or as described below under "Hyperproliferative Disorders").

[363] In specific embodiments, a protein, nucleic acid, or antibody of the invention (or fragment or variant thereof) having a "Cancer" recitation in the "Preferred Indication" column of Table 1D may be used for example, to diagnose, treat, prevent, and/or ameliorate a neoplasm located in a tissue selected from the group consisting of: colon, abdomen, bone, breast, digestive system, liver, pancreas, prostate, peritoneum, lung, blood (e.g., leukemia), endocrine glands (adrenal, parathyroid, pituitary, testicles, ovary, thymus, thyroid), uterus, eye, head and neck, nervous (central and peripheral), lymphatic system, pelvic, skin, soft tissue, spleen, thoracic, and urogenital.

[364] In specific embodiments, a protein, nucleic acid, or antibody of the invention (or fragment or variant thereof) having a "Cancer" recitation in the "Preferred Indication" column of Table 1D, may be used for example, to diagnose, treat, prevent, and/or ameliorate a pre-neoplastic condition, selected from the group consisting of: hyperplasia (e.g., endometrial hyperplasia and/or as described in the section entitled "Hyperproliferative Disorders"), metaplasia (e.g., connective tissue metaplasia, atypical metaplasia, and/or as described in the section entitled "Hyperproliferative Disorders"), and/or dysplasia (e.g., cervical dysplasia, and bronchopulmonary dysplasia).

[365] In another specific embodiment, a protein, nucleic acid, or antibody of the invention (or fragment or variant thereof) having a "Cancer" recitation in the "Preferred Indication" column of Table 1D, may be used for example, to diagnose, treat, prevent, and/or ameliorate a benign dysproliferative disorder selected from the group consisting of: benign tumors, fibrocystic conditions, tissue hypertrophy, and/or as described in the section entitled "Hyperproliferative Disorders".

[366] The recitation of "Immune/Hematopoietic" in the "Preferred Indication" column indicates that the corresponding nucleic acid and protein, or antibody against the same, of the invention (or fragment or variant thereof), may be used for example, to diagnose, treat, prevent, and/or ameliorate diseases and/or disorders relating to neoplastic diseases (e.g., as described below under "Hyperproliferative Disorders"), blood disorders (e.g., as described below under "Immune Activity" "Cardiovascular Disorders" and/or "Blood-Related Disorders"), and infections (e.g., as described below under "Infectious Disease").

[367] In specific embodiments, a protein, nucleic acid, or antibody of the invention (or fragment or variant thereof) having the "Immune/Hematopoietic" recitation in the "Preferred Indication" column of Table 1D, may be used for example, to diagnose, treat, prevent, and/or ameliorate a disease or disorder selected from the group consisting of: anemia, pancytopenia, leukopenia, thrombocytopenia, leukemias, Hodgkin's disease, non-

Hodgkin's lymphoma, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, asthma, AIDS, autoimmune disease, rheumatoid arthritis, granulomatous disease, immune deficiency, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, immune reactions to transplanted organs and tissues, systemic lupus erythematosis, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, Lyme Disease, and allergies.

The recitation of "Reproductive" in the "Preferred Indication" column indicates that the corresponding nucleic acid and protein, or antibody against the same, of the invention (or fragment or variant thereof), may be used for example, to diagnose, treat, prevent, and/or ameliorate diseases and/or disorders relating to neoplastic diseases (e.g., as described below under "Hyperproliferative Disorders"), and disorders of the reproductive system (e.g., as described below under "Reproductive System Disorders").

[369] In specific embodiments, a protein, nucleic acid, or antibody of the invention (or fragment or variant thereof) having a "Reproductive" recitation in the "Preferred Indication" column of Table 1D, may be used for example, to diagnose, treat, prevent, and/or ameliorate a disease or disorder selected from the group consisting of: cryptorchism, prostatitis, inguinal hernia, varicocele, leydig cell tumors, verrucous carcinoma, prostatitis, malacoplakia, Peyronie's disease, penile carcinoma, squamous cell hyperplasia, dysmenorrhea, ovarian adenocarcinoma, Turner's syndrome, mucopurulent cervicitis, Sertoli-leydig tumors, ovarian cancer, uterine cancer, pelvic inflammatory disease, testicular cancer, prostate cancer, Klinefelter's syndrome, Young's syndrome, premature ejaculation, diabetes mellitus, cystic fibrosis, Kartagener's syndrome, testicular atrophy, testicular feminization, anorchia, ectopic testis, epididymitis, orchitis, gonorrhea, syphilis, testicular torsion, vasitis nodosa, germ cell tumors, stromal tumors, dysmenorrhea, endometriosis, fibroids, adenomyosis, anovulatory bleeding, retroverted uterus, amenorrhea, Cushing's syndrome, hydatidiform moles, Asherman's syndrome, premature menopause, precocious puberty, uterine polyps, dysfunctional uterine bleeding, cervicitis, chronic cervicitis, mucopurulent cervicitis, cervical dysplasia, cervical polyps, Nabothian cysts, cervical erosion, cervical incompetence, cervical neoplasms, pseudohermaphroditism, and premenstrual syndrome.

[370] The recitation of "Musculoskeletal" in the "Preferred Indication" column indicates that the corresponding nucleic acid and protein, or antibody against the same, of the invention (or fragment or variant thereof), may be used for example, to diagnose, treat, prevent, and/or ameliorate diseases and/or disorders relating to neoplastic diseases (e.g., as

described below under "Hyperproliferative Disorders"), and disorders of the immune system (e.g., as described below under "Immune Activity").

[371] In specific embodiments, a protein, nucleic acid, or antibody of the invention (or fragment or variant thereof) having a "Musculoskeletal" recitation in the "Preferred Indication" column of Table 1D, may be used for example, to diagnose, treat, prevent, and/or ameliorate a disease or disorder selected from the group consisting of: bone cancers (e.g., osteochondromas, benign chondromas, chondroblastoma, chondromyxoid fibromas, osteoid osteomas, giant cell tumors, multiple myeloma, osteosarcomas), Paget's Disease, rheumatoid arthritis, systemic lupus erythematosus, osteomyelitis, Lyme Disease, gout, bursitis, tendonitis, osteoporosis, osteoarthritis, muscular dystrophy, mitochondrial myopathy, cachexia, and multiple sclerosis.

[372] The recitation of "Cardiovascular" in the "Preferred Indication" column indicates that the corresponding nucleic acid and protein, or antibody against the same, of the invention (or fragment or variant thereof), may be used for example, to diagnose, treat, prevent, and/or ameliorate diseases and/or disorders relating to neoplastic diseases (e.g., as described below under "Hyperproliferative Disorders"), and disorders of the cardiovascular system (e.g., as described below under "Cardiovascular Disorders").

[373] In specific embodiments, a protein, nucleic acid, or antibody of the invention (or fragment or variant thereof) having a "Cardiovascular" recitation in the "Preferred Indication" column of Table 1D, may be used for example, to diagnose, treat, prevent, and/or ameliorate a disease or disorder selected from the group consisting of: myxomas, fibromas, rhabdomyomas, cardiovascular abnormalities (e.g., congenital heart defects, cerebral arteriovenous malformations, septal defects), heart disease (e.g., heart failure, congestive heart disease, arrhythmia, tachycardia, fibrillation, pericardial Disease, endocarditis), cardiac arrest, heart valve disease (e.g., stenosis, regurgitation, prolapse), vascular disease (e.g., hypertension, coronary artery disease, angina, aneurysm, arteriosclerosis, peripheral vascular disease), hyponatremia, hypernatremia, hypokalemia, and hyperkalemia.

[374] The recitation of "Mixed Fetal" in the "Preferred Indication" column indicates that the corresponding nucleic acid and protein, or antibody against the same, of the invention (or fragment or variant thereof), may be used for example, to diagnose, treat, prevent, and/or ameliorate diseases and/or disorders relating to neoplastic diseases (e.g., as described below under "Hyperproliferative Disorders").

[375] In specific embodiments, a protein, nucleic acid, or antibody of the invention (or fragment or variant thereof) having a "Mixed Fetal" recitation in the "Preferred Indication" column of Table 1D, may be used for example, to diagnose, treat, prevent, and/or ameliorate a disease or disorder selected from the group consisting of: spina bifida, hydranencephaly, neurofibromatosis, fetal alcohol syndrome, diabetes mellitus, PKU, Down's syndrome, Patau syndrome, Edwards syndrome, Turner syndrome, Apert syndrome, Carpenter syndrome, Conradi syndrome, Crouzon syndrome, cutis laxa, Cornelia de Lange syndrome, Ellis-van Creveld syndrome, Holt-Oram syndrome, Kartagener syndrome, Meckel-Gruber syndrome, Noonan syndrome, Pallister-Hall syndrome, Rubinstein-Taybi syndrome, Scimitar syndrome, Smith-Lemli-Opitz syndrome, thromocytopenia-absent radius (TAR) syndrome, Treacher Collins syndrome, Williams syndrome, Hirschsprung's disease, Meckel's diverticulum, polycystic kidney disease, Turner's syndrome, and gonadal dysgenesis, Klippel-Feil syndrome, Ostogenesis imperfecta, muscular dystrophy, Tay-Sachs disease, Wilm's tumor, neuroblastoma, and retinoblastoma.

[376] The recitation of "Excretory" in the "Preferred Indication" column indicates that the corresponding nucleic acid and protein, or antibody against the same, of the invention (or fragment or variant thereof), may be used for example, to diagnose, treat, prevent, and/or ameliorate diseases and/or disorders relating to neoplastic diseases (e.g., as described below under "Hyperproliferative Disorders") and renal disorders (e.g., as described below under "Renal Disorders").

[377] In specific embodiments, a protein, nucleic acid, or antibody of the invention (or fragment or variant thereof) having a "Excretory" recitation in the "Preferred Indication" column of Table 1D, may be used for example, to diagnose, treat, prevent, and/or ameliorate a disease or disorder selected from the group consisting of: bladder cancer, prostate cancer, benign prostatic hyperplasia, bladder disorders (e.g., urinary incontinence, urinary retention, urinary obstruction, urinary tract Infections, interstitial cystitis, prostatitis, neurogenic bladder, hematuria), renal disorders (e.g., hydronephrosis, proteinuria, renal failure, pyelonephritis, urolithiasis, reflux nephropathy, and unilateral obstructive uropathy).

[378] The recitation of "Neural/Sensory" in the "Preferred Indication" column indicates that the corresponding nucleic acid and protein, or antibody against the same, of the invention (or fragment or variant thereof), may be used for example, to diagnose, treat, prevent, and/or ameliorate diseases and/or disorders relating to neoplastic diseases (e.g., as

described below under "Hyperproliferative Disorders") and diseases or disorders of the nervous system (e.g., as described below under "Neural Activity and Neurological Diseases").

[379] In specific embodiments, a protein, nucleic acid, or antibody of the invention (or fragment or variant thereof) having a "Neural/Sensory" recitation in the "Preferred Indication" column of Table 1D, may be used for example, to diagnose, treat, prevent, and/or ameliorate a disease or disorder selected from the group consisting of: brain cancer (e.g., brain stem glioma, brain tumors, central nervous system (Primary) lymphoma, central nervous system lymphoma, cerebellar astrocytoma, and cerebral astrocytoma, neurodegenerative disorders (e.g., Alzheimer's Disease, Creutzfeldt-Jakob Disease, Parkinson's Disease, and Idiopathic Presenile Dementia), encephalomyelitis, cerebral malaria, meningitis, metabolic brain diseases (e.g., phenylketonuria and pyruvate carboxylase deficiency), cerebellar ataxia, ataxia telangiectasia, and AIDS Dementia Complex, schizophrenia, attention deficit disorder, hyperactive attention deficit disorder, autism, and obsessive compulsive disorders.

[380] The recitation of "Respiratory" in the "Preferred Indication" column indicates that the corresponding nucleic acid and protein, or antibody against the same, of the invention (or fragment or variant thereof), may be used for example, to diagnose, treat, prevent, and/or ameliorate diseases and/or disorders relating to neoplastic diseases (e.g., as described below under "Hyperproliferative Disorders") and diseases or disorders of the respiratory system (e.g., as described below under "Respiratory Disorders").

[381] In specific embodiments, a protein, nucleic acid, or antibody of the invention (or fragment or variant thereof) having a "Respiratory" recitation in the "Preferred Indication" column of Table 1D, may be used for example, to diagnose, treat, prevent, and/or ameliorate a disease or disorder selected from the group consisting of: cancers of the respiratory system such as larynx cancer, pharynx cancer, trachea cancer, epiglottis cancer, lung cancer, squamous cell carcinomas, small cell (oat cell) carcinomas, large cell carcinomas, and adenocarcinomas. Allergic reactions, cystic fibrosis, sarcoidosis, histiocytosis X, infiltrative lung diseases (e.g., pulmonary fibrosis and lymphoid interstitial pneumonia), obstructive airway diseases (e.g., asthma, emphysema, chronic or acute bronchitis), occupational lung diseases (e.g., silicosis and asbestosis), pneumonia, and pleurisy.

[382] The recitation of "Endocrine" in the "Preferred Indication" column indicates that the corresponding nucleic acid and protein, or antibody against the same, of the invention

(or fragment or variant thereof), may be used for example, to diagnose, treat, prevent, and/or ameliorate diseases and/or disorders relating to neoplastic diseases (e.g., as described below under "Hyperproliferative Disorders") and diseases or disorders of the respiratory system (e.g., as described below under "Respiratory Disorders"), renal disorders (e.g., as described below under "Renal Disorders"), and disorders of the endocrine system (e.g., as described below under "Endocrine Disorders".

In specific embodiments, a protein, nucleic acid, or antibody of the invention (or [383] fragment or variant thereof) having an "Endocrine" recitation in the "Preferred Indication" column of Table 1D, may be used for example, to diagnose, treat, prevent, and/or ameliorate a disease or disorder selected from the group consisting of: cancers of endocrine tissues and organs (e.g., cancers of the hypothalamus, pituitary gland, thyroid gland, parathyroid glands, pancreas, adrenal glands, ovaries, and testes), diabetes (e.g., diabetes insipidus, type I and type II diabetes mellitus), obesity, disorders related to pituitary glands (e.g., hyperpituitarism, hypopituitarism, and pituitary dwarfism), hypothyroidism, hyperthyroidism, goiter, reproductive disorders (e.g. male and female infertility), disorders related to adrenal glands (e.g., Addison's Disease, corticosteroid deficiency, and Cushing's Syndrome), kidney cancer (e.g., hypernephroma, transitional cell cancer, and Wilm's interstitial nephritis, polycystic kidney nephropathy, diabetic tumor), glomerulonephritis proliferative (e.g., mesangial glomerulonephritis IgM glomerulonephritis caused by autoimmune disorders; such as Goodpasture's syndrome), and nephrocalcinosis.

[384] The recitation of "Digestive" in the "Preferred Indication" column indicates that the corresponding nucleic acid and protein, or antibody against the same, of the invention (or fragment or variant thereof), may be used for example, to diagnose, treat, prevent, and/or ameliorate diseases and/or disorders relating to neoplastic diseases (e.g., as described below under "Hyperproliferative Disorders") and diseases or disorders of the gastrointestinal system (e.g., as described below under "Gastrointestinal Disorders".

[385] In specific embodiments, a protein, nucleic acid, or antibody of the invention (or fragment or variant thereof) having a "Digestive" recitation in the "Preferred Indication" column of Table 1D, may be used for example, to diagnose, treat, prevent, and/or ameliorate a disease or disorder selected from the group consisting of: ulcerative colitis, appendicitis, Crohn's disease, hepatitis, hepatic encephalopathy, portal hypertension, cholelithiasis, cancer of the digestive system (e.g., biliary tract cancer, stomach cancer, colon cancer, gastric cancer, pancreatic cancer, cancer of the bile duct, tumors of the colon

(e.g., polyps or cancers), and cirrhosis), pancreatitis, ulcerative disease, pyloric stenosis, gastroenteritis, gastritis, gastric atropy, benign tumors of the duodenum, distension, irritable bowel syndrome, malabsorption, congenital disorders of the small intestine, bacterial and parasitic infection, megacolon, Hirschsprung's disease, aganglionic megacolon, acquired megacolon, colitis, anorectal disorders (e.g., anal fistulas, hemorrhoids), congenital disorders of the liver (e.g., Wilson's disease, hemochromatosis, cystic fibrosis, biliary atresia, and alpha1-antitrypsin deficiency), portal hypertension, cholelithiasis, and jaundice.

[386] The recitation of "Connective/Epithelial" in the "Preferred Indication" column indicates that the corresponding nucleic acid and protein, or antibody against the same, of the invention (or fragment or variant thereof), may be used for example, to diagnose, treat, prevent, and/or ameliorate diseases and/or disorders relating to neoplastic diseases (e.g., as described below under "Hyperproliferative Disorders"), cellular and genetic abnormalities (e.g., as described below under "Diseases at the Cellular Level "), angiogenesis (e.g., as described below under "Anti-Angiogenesis Activity "), and or to promote or inhibit regeneration (e.g., as described below under "Regeneration "), and wound healing (e.g., as described below under "Wound Healing and Epithelial Cell Proliferation").

In specific embodiments, a protein, nucleic acid, or antibody of the invention (or [387] fragment or variant thereof) having a "Connective/Epithelial" recitation in the "Preferred Indication" column of Table 1D, may be used for example, to diagnose, treat, prevent, and/or ameliorate a disease or disorder selected from the group consisting of: connective tissue metaplasia, mixed connective tissue disease, focal epithelial hyperplasia, epithelial metaplasia, mucoepithelial dysplasia, graft v. host disease, polymyositis, cystic hyperplasia, cerebral dysplasia, tissue hypertrophy, Alzheimer's disease, lymphoproliferative disorder, Waldenstron's macroglobulinemia, Crohn's disease, pernicious anemia, idiopathic Addison's disease, glomerulonephritis, bullous pemphigoid, Sjogren's syndrome, diabetes mellitus, cystic fibrosis, osteoblastoma, osteoclastoma, osteosarcoma, chondrosarcoma, osteoporosis, osteocarthritis, periodontal disease, wound healing, relapsing polychondritis, vasculitis, polyarteritis nodosa, Wegener's granulomatosis, cellulitis, rheumatoid arthritis, psoriatic arthritis, discoid lupus erythematosus, systemic lupus erythematosus, scleroderma, CREST syndrome, Sjogren's syndrome, polymyositis, dermatomyositis, mixed connective tissue disease, relapsing polychondritis, vasculitis, Henoch-Schonlein syndrome, erythema nodosum, polyarteritis nodosa, temporal (giant cell) arteritis, Takayasu's arteritis, Wegener's granulomatosis, Reiter's syndrome, Behcet's syndrome, ankylosing spondylitis, cellulitis, keloids, Ehler Danlos syndrome, Marfan syndrome, pseudoxantoma elasticum, osteogenese imperfecta, chondrodysplasias, epidermolysis bullosa, Alport syndrome, and cutis laxa.

Table 1E also provides information regarding biological activities and preferred [388] therapeutic uses (i.e. see, "Preferred Indications" column) for polynucleotides and polypeptides of the invention (including antibodies, agonists, and/or antagonists thereof). Table 1E also provides information regarding assays which may be used to test polynucleotides and polypeptides of the invention (including antibodies, agonists, and/or antagonists thereof) for the corresponding biological activities. The first column ("Gene No.") provides the gene number in the application for each clone identifier. The second column ("cDNA Clone ID No:Z") provides the unique clone identifier for each clone as previously described and indicated in Tables 1A, 1B, 1C, and 1D. The third column ("AA SEQ ID NO:Y") indicates the Sequence Listing SEQ ID Number for polypeptide sequences encoded by the corresponding cDNA clones (also as indicated in Tables 1A, 1B, and 2). The fourth column ("Biological Activity") indicates a biological activity corresponding to the indicated polypeptides (or polynucleotides encoding said polypeptides). The fifth column ("Exemplary Activity Assay") further describes the corresponding biological activity and also provides information pertaining to the various types of assays which may be performed to test, demonstrate, or quantify the corresponding biological activity. The sixth column ("Preferred Indications") describes particular embodiments of the invention as well as indications (e.g. pathologies, diseases, disorders, abnormalities, etc.) for which polynucleotides and polypeptides of the invention (including antibodies, agonists, and/or antagonists thereof) may be used in detecting, diagnosing, preventing, and/or treating.

[389] The present invention is further directed to antibody-based therapies which involve administering antibodies of the invention to an animal, preferably a mammal, and most preferably a human, patient for treating one or more of the disclosed diseases, disorders, or conditions. Therapeutic compounds of the invention include, but are not limited to, antibodies of the invention (including fragments, analogs and derivatives thereof as described herein) and nucleic acids encoding antibodies of the invention (including fragments, analogs and derivatives thereof and anti-idiotypic antibodies as described herein). The antibodies of the invention can be used to treat, inhibit or prevent diseases, disorders or conditions associated with aberrant expression and/or activity of a polypeptide of the invention, including, but not limited to, any one or more of the diseases, disorders, or conditions described herein. The treatment and/or prevention of diseases, disorders, or

conditions associated with aberrant expression and/or activity of a polypeptide of the invention includes, but is not limited to, alleviating symptoms associated with those diseases, disorders or conditions. Antibodies of the invention may be provided in pharmaceutically acceptable compositions as known in the art or as described herein.

In a specific and preferred embodiment, the present invention is directed to [390] antibody-based therapies which involve administering antibodies of the invention to an animal, preferably a mammal, and most preferably a human, patient for treating one or more diseases, disorders, or conditions, including but not limited to: neural disorders, immune system disorders, muscular disorders, reproductive disorders, gastrointestinal disorders, pulmonary disorders, cardiovascular disorders, renal disorders, proliferative disorders, and/or cancerous diseases and conditions., and/or as described elsewhere herein. Therapeutic compounds of the invention include, but are not limited to, antibodies of the invention (e.g., antibodies directed to the full length protein expressed on the cell surface of a mammalian cell; antibodies directed to an epitope of a polypeptide of the invention (such as, for example, a predicted linear epitope shown in column 7 of Table 1B; or a conformational epitope, including fragments, analogs and derivatives thereof as described herein) and nucleic acids encoding antibodies of the invention (including fragments, analogs and derivatives thereof and anti-idiotypic antibodies as described herein). The antibodies of the invention can be used to treat, inhibit or prevent diseases, disorders or conditions associated with aberrant expression and/or activity of a polypeptide of the invention, including, but not limited to, any one or more of the diseases, disorders, or conditions described herein. The treatment and/or prevention of diseases, disorders, or conditions associated with aberrant expression and/or activity of a polypeptide of the invention includes, but is not limited to, alleviating symptoms associated with those diseases, disorders or conditions. Antibodies of the invention may be provided in pharmaceutically acceptable compositions as known in the art or as described herein.

[391] A summary of the ways in which the antibodies of the present invention may be used therapeutically includes binding polynucleotides or polypeptides of the present invention locally or systemically in the body or by direct cytotoxicity of the antibody, e.g. as mediated by complement (CDC) or by effector cells (ADCC). Some of these approaches are described in more detail below. Armed with the teachings provided herein, one of ordinary skill in the art will know how to use the antibodies of the present invention for diagnostic, monitoring or therapeutic purposes without undue experimentation.

[392] The antibodies of this invention may be advantageously utilized in combination with other monoclonal or chimeric antibodies, or with lymphokines or hematopoietic growth factors (such as, e.g., IL-2, IL-3 and IL-7), for example, which serve to increase the number or activity of effector cells which interact with the antibodies.

[393] The antibodies of the invention may be administered alone or in combination with other types of treatments (e.g., radiation therapy, chemotherapy, hormonal therapy, immunotherapy and anti-tumor agents). Generally, administration of products of a species origin or species reactivity (in the case of antibodies) that is the same species as that of the patient is preferred. Thus, in a preferred embodiment, human antibodies, fragments derivatives, analogs, or nucleic acids, are administered to a human patient for therapy or prophylaxis.

[394] It is preferred to use high affinity and/or potent *in vivo* inhibiting and/or neutralizing antibodies against polypeptides or polynucleotides of the present invention, fragments or regions thereof, for both immunoassays directed to and therapy of disorders related to polynucleotides or polypeptides, including fragments thereof, of the present invention. Such antibodies, fragments, or regions, will preferably have an affinity for polynucleotides or polypeptides of the invention, including fragments thereof. Preferred binding affinities include those with a dissociation constant or Kd less than 5 X 10⁻² M, 10⁻² M, 5 X 10⁻³ M, 10⁻³ M, 5 X 10⁻⁴ M, 10⁻⁴ M, 5 X 10⁻⁵ M, 10⁻⁵ M, 5 X 10⁻⁶ M, 10⁻⁶ M, 5 X 10⁻¹⁷ M, 5 X 10⁻¹⁸ M, 10⁻⁸ M, 5 X 10⁻¹⁹ M, 10⁻¹⁹ M, 5 X 10⁻¹⁰ M, 10⁻¹⁰ M, 5 X 10⁻¹¹ M, 10⁻¹¹ M, 5 X 10⁻¹² M, 10⁻¹² M, 5 X 10⁻¹³ M, 10⁻¹³ M, 10⁻¹⁴ M, 5 X 10⁻¹⁵ M, and 10⁻¹⁵ M.

Gene Therapy

[395] In a specific embodiment, nucleic acids comprising sequences encoding antibodies or functional derivatives thereof, are administered to treat, inhibit or prevent a disease or disorder associated with aberrant expression and/or activity of a polypeptide of the invention, by way of gene therapy. Gene therapy refers to therapy performed by the administration to a subject of an expressed or expressible nucleic acid. In this embodiment of the invention, the nucleic acids produce their encoded protein that mediates a therapeutic effect.

[396] Any of the methods for gene therapy available in the art can be used according to the present invention. Exemplary methods are described below.

[397] For general reviews of the methods of gene therapy, see Goldspiel et al., Clinical Pharmacy 12:488-505 (1993); Wu and Wu, Biotherapy 3:87-95 (1991); Tolstoshev, Ann. Rev. Pharmacol. Toxicol. 32:573-596 (1993); Mulligan, Science 260:926-932 (1993); and Morgan and Anderson, Ann. Rev. Biochem. 62:191-217 (1993); May, TIBTECH 11(5):155-215 (1993). Methods commonly known in the art of recombinant DNA technology which can be used are described in Ausubel et al. (eds.), Current Protocols in Molecular Biology, John Wiley & Sons, NY (1993); and Kriegler, Gene Transfer and Expression, A Laboratory Manual, Stockton Press, NY (1990).

[398] In a preferred embodiment, the compound comprises nucleic acid sequences encoding an antibody, said nucleic acid sequences being part of expression vectors that express the antibody or fragments or chimeric proteins or heavy or light chains thereof in a suitable host. In particular, such nucleic acid sequences have promoters operably linked to the antibody coding region, said promoter being inducible or constitutive, and, optionally, tissue-specific. In another particular embodiment, nucleic acid molecules are used in which the antibody coding sequences and any other desired sequences are flanked by regions that promote homologous recombination at a desired site in the genome, thus providing for intrachromosomal expression of the antibody encoding nucleic acids (Koller and Smithies, Proc. Natl. Acad. Sci. USA 86:8932-8935 (1989); Zijlstra et al., Nature 342:435-438 (1989). In specific embodiments, the expressed antibody molecule is a single chain antibody; alternatively, the nucleic acid sequences include sequences encoding both the heavy and light chains, or fragments thereof, of the antibody.

[399] Delivery of the nucleic acids into a patient may be either direct, in which case the patient is directly exposed to the nucleic acid or nucleic acid- carrying vectors, or indirect, in which case, cells are first transformed with the nucleic acids in vitro, then transplanted into the patient. These two approaches are known, respectively, as *in vivo* or ex vivo gene therapy.

[400] In a specific embodiment, the nucleic acid sequences are directly administered *in vivo*, where it is expressed to produce the encoded product. This can be accomplished by any of numerous methods known in the art, e.g., by constructing them as part of an appropriate nucleic acid expression vector and administering it so that they become intracellular, e.g., by infection using defective or attenuated retrovirals or other viral vectors (see U.S. Patent No. 4,980,286), or by direct injection of naked DNA, or by use of microparticle bombardment (e.g., a gene gun; Biolistic, Dupont), or coating with lipids or

cell-surface receptors or transfecting agents, encapsulation in liposomes, microparticles, or microcapsules, or by administering them in linkage to a peptide which is known to enter the nucleus, by administering it in linkage to a ligand subject to receptor-mediated endocytosis (see, e.g., Wu and Wu, J. Biol. Chem. 262:4429-4432 (1987)) (which can be used to target cell types specifically expressing the receptors), etc. In another embodiment, nucleic acid-ligand complexes can be formed in which the ligand comprises a fusogenic viral peptide to disrupt endosomes, allowing the nucleic acid to avoid lysosomal degradation. In yet another embodiment, the nucleic acid can be targeted *in vivo* for cell specific uptake and expression, by targeting a specific receptor (see, e.g., PCT Publications WO 92/06180; WO 92/22635; WO92/20316; WO93/14188, WO 93/20221). Alternatively, the nucleic acid can be introduced intracellularly and incorporated within host cell DNA for expression, by homologous recombination (Koller and Smithies, Proc. Natl. Acad. Sci. USA 86:8932-8935 (1989); Zijlstra et al., Nature 342:435-438 (1989)).

[401] In a specific embodiment, viral vectors that contains nucleic acid sequences encoding an antibody of the invention are used. For example, a retroviral vector can be used (see Miller et al., Meth. Enzymol. 217:581-599 (1993)). These retroviral vectors contain the components necessary for the correct packaging of the viral genome and integration into the host cell DNA. The nucleic acid sequences encoding the antibody to be used in gene therapy are cloned into one or more vectors, which facilitates delivery of the gene into a patient. More detail about retroviral vectors can be found in Boesen et al., Biotherapy 6:291-302 (1994), which describes the use of a retroviral vector to deliver the mdr1 gene to hematopoietic stem cells in order to make the stem cells more resistant to chemotherapy. Other references illustrating the use of retroviral vectors in gene therapy are: Clowes et al., J. Clin. Invest. 93:644-651 (1994); Kiem et al., Blood 83:1467-1473 (1994); Salmons and Gunzberg, Human Gene Therapy 4:129-141 (1993); and Grossman and Wilson, Curr. Opin. in Genetics and Devel. 3:110-114 (1993).

[402] Adenoviruses are other viral vectors that can be used in gene therapy. Adenoviruses are especially attractive vehicles for delivering genes to respiratory epithelia. Adenoviruses naturally infect respiratory epithelia where they cause a mild disease. Other targets for adenovirus-based delivery systems are liver, the central nervous system, endothelial cells, and muscle. Adenoviruses have the advantage of being capable of infecting non-dividing cells. Kozarsky and Wilson, Current Opinion in Genetics and Development 3:499-503 (1993) present a review of adenovirus-based gene therapy. Bout et

al., Human Gene Therapy 5:3-10 (1994) demonstrated the use of adenovirus vectors to transfer genes to the respiratory epithelia of rhesus monkeys. Other instances of the use of adenoviruses in gene therapy can be found in Rosenfeld et al., Science 252:431-434 (1991); Rosenfeld et al., Cell 68:143- 155 (1992); Mastrangeli et al., J. Clin. Invest. 91:225-234 (1993); PCT Publication WO94/12649; and Wang, et al., Gene Therapy 2:775-783 (1995). In a preferred embodiment, adenovirus vectors are used.

[403] Adeno-associated virus (AAV) has also been proposed for use in gene therapy (Walsh et al., Proc. Soc. Exp. Biol. Med. 204:289-300 (1993); U.S. Patent No. 5,436,146).

[404] Another approach to gene therapy involves transferring a gene to cells in tissue culture by such methods as electroporation, lipofection, calcium phosphate mediated transfection, or viral infection. Usually, the method of transfer includes the transfer of a selectable marker to the cells. The cells are then placed under selection to isolate those cells that have taken up and are expressing the transferred gene. Those cells are then delivered to a patient.

[405] In this embodiment, the nucleic acid is introduced into a cell prior to administration *in vivo* of the resulting recombinant cell. Such introduction can be carried out by any method known in the art, including but not limited to transfection, electroporation, microinjection, infection with a viral or bacteriophage vector containing the nucleic acid sequences, cell fusion, chromosome-mediated gene transfer, microcell-mediated gene transfer, spheroplast fusion, etc. Numerous techniques are known in the art for the introduction of foreign genes into cells (see, e.g., Loeffler and Behr, Meth. Enzymol. 217:599-618 (1993); Cohen et al., Meth. Enzymol. 217:618-644 (1993); Cline, Pharmac. Ther. 29:69-92m (1985) and may be used in accordance with the present invention, provided that the necessary developmental and physiological functions of the recipient cells are not disrupted. The technique should provide for the stable transfer of the nucleic acid to the cell, so that the nucleic acid is expressible by the cell and preferably heritable and expressible by its cell progeny.

[406] The resulting recombinant cells can be delivered to a patient by various methods known in the art. Recombinant blood cells (e.g., hematopoietic stem or progenitor cells) are preferably administered intravenously. The amount of cells envisioned for use depends on the desired effect, patient state, etc., and can be determined by one skilled in the art.

[407] Cells into which a nucleic acid can be introduced for purposes of gene therapy encompass any desired, available cell type, and include but are not limited to epithelial

cells, endothelial cells, keratinocytes, fibroblasts, muscle cells, hepatocytes; blood cells such as T lymphocytes, B lymphocytes, monocytes, macrophages, neutrophils, eosinophils, megakaryocytes, granulocytes; various stem or progenitor cells, in particular hematopoietic stem or progenitor cells, e.g., as obtained from bone marrow, umbilical cord blood, peripheral blood, fetal liver, etc.

[408] In a preferred embodiment, the cell used for gene therapy is autologous to the patient.

[409] In an embodiment in which recombinant cells are used in gene therapy, nucleic acid sequences encoding an antibody are introduced into the cells such that they are expressible by the cells or their progeny, and the recombinant cells are then administered in vivo for therapeutic effect. In a specific embodiment, stem or progenitor cells are used. Any stem and/or progenitor cells which can be isolated and maintained in vitro can potentially be used in accordance with this embodiment of the present invention (see e.g. PCT Publication WO 94/08598; Stemple and Anderson, Cell 71:973-985 (1992); Rheinwald, Meth. Cell Bio. 21A:229 (1980); and Pittelkow and Scott, Mayo Clinic Proc. 61:771 (1986)).

[410] In a specific embodiment, the nucleic acid to be introduced for purposes of gene therapy comprises an inducible promoter operably linked to the coding region, such that expression of the nucleic acid is controllable by the presence or absence of an appropriate inducer of transcription.

Demonstration of Therapeutic or Prophylactic Activity

[411] The compounds or pharmaceutical compositions of the invention are preferably tested in vitro, and then *in vivo* for the desired therapeutic or prophylactic activity, prior to use in humans. For example, in vitro assays to demonstrate the therapeutic or prophylactic utility of a compound or pharmaceutical composition include, the effect of a compound on a cell line or a patient tissue sample. The effect of the compound or composition on the cell line and/or tissue sample can be determined utilizing techniques known to those of skill in the art including, but not limited to, rosette formation assays and cell lysis assays. In accordance with the invention, in vitro assays which can be used to determine whether administration of a specific compound is indicated, include in vitro cell culture assays in which a patient tissue sample is grown in culture, and exposed to or otherwise administered a compound, and the effect of such compound upon the tissue sample is observed.

Therapeutic/Prophylactic Administration and Composition

[412] The invention provides methods of treatment, inhibition and prophylaxis by administration to a subject of an effective amount of a compound or pharmaceutical composition of the invention, preferably a polypeptide or antibody of the invention. In a preferred embodiment, the compound is substantially purified (e.g., substantially free from substances that limit its effect or produce undesired side-effects). The subject is preferably an animal, including but not limited to animals such as cows, pigs, horses, chickens, cats, dogs, etc., and is preferably a mammal, and most preferably human.

[413] Formulations and methods of administration that can be employed when the compound comprises a nucleic acid or an immunoglobulin are described above; additional appropriate formulations and routes of administration can be selected from among those described herein below.

Various delivery systems are known and can be used to administer a compound [414] of the invention, e.g., encapsulation in liposomes, microparticles, microcapsules, recombinant cells capable of expressing the compound, receptor-mediated endocytosis (see, e.g., Wu and Wu, J. Biol. Chem. 262:4429-4432 (1987)), construction of a nucleic acid as part of a retroviral or other vector, etc. Methods of introduction include but are not limited intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural, and oral routes. The compounds or compositions may be administered by any convenient route, for example by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (e.g., oral mucosa, rectal and intestinal mucosa, etc.) and may be administered together with other biologically active agents. Administration can In addition, it may be desirable to introduce the pharmaceutical be systemic or local. compounds or compositions of the invention into the central nervous system by any suitable route, including intraventricular and intrathecal injection; intraventricular injection may be facilitated by an intraventricular catheter, for example, attached to a reservoir, such as an Ommaya reservoir. Pulmonary administration can also be employed, e.g., by use of an inhaler or nebulizer, and formulation with an aerosolizing agent.

[415] In a specific embodiment, it may be desirable to administer the pharmaceutical compounds or compositions of the invention locally to the area in need of treatment; this may be achieved by, for example, and not by way of limitation, local infusion during surgery, topical application, e.g., in conjunction with a wound dressing after surgery, by

injection, by means of a catheter, by means of a suppository, or by means of an implant, said implant being of a porous, non-porous, or gelatinous material, including membranes, such as sialastic membranes, or fibers. Preferably, when administering a protein, including an antibody, of the invention, care must be taken to use materials to which the protein does not absorb.

[416] In another embodiment, the compound or composition can be delivered in a vesicle, in particular a liposome (see Langer, Science 249:1527-1533 (1990); Treat et al., in Liposomes in the Therapy of Infectious Disease and Cancer, Lopez-Berestein and Fidler (eds.), Liss, New York, pp. 353- 365 (1989); Lopez-Berestein, ibid., pp. 317-327; see generally ibid.)

[417] In yet another embodiment, the compound or composition can be delivered in a controlled release system. In one embodiment, a pump may be used (see Langer, *supra*; Sefton, CRC Crit. Ref. Biomed. Eng. 14:201 (1987); Buchwald et al., Surgery 88:507 (1980); Saudek et al., N. Engl. J. Med. 321:574 (1989)). In another embodiment, polymeric materials can be used (see Medical Applications of Controlled Release, Langer and Wise (eds.), CRC Pres., Boca Raton, Florida (1974); Controlled Drug Bioavailability, Drug Product Design and Performance, Smolen and Ball (eds.), Wiley, New York (1984); Ranger and Peppas, J., Macromol. Sci. Rev. Macromol. Chem. 23:61 (1983); see also Levy et al., Science 228:190 (1985); During et al., Ann. Neurol. 25:351 (1989); Howard et al., J.Neurosurg. 71:105 (1989)). In yet another embodiment, a controlled release system can be placed in proximity of the therapeutic target, e.g., the brain, thus requiring only a fraction of the systemic dose (see, e.g., Goodson, in Medical Applications of Controlled Release, *supra*, vol. 2, pp. 115-138 (1984)).

[418] Other controlled release systems are discussed in the review by Langer (Science 249:1527-1533 (1990)).

[419] In a specific embodiment where the compound of the invention is a nucleic acid encoding a protein, the nucleic acid can be administered *in vivo* to promote expression of its encoded protein, by constructing it as part of an appropriate nucleic acid expression vector and administering it so that it becomes intracellular, e.g., by use of a retroviral vector (see U.S. Patent No. 4,980,286), or by direct injection, or by use of microparticle bombardment (e.g., a gene gun; Biolistic, Dupont), or coating with lipids or cell-surface receptors or transfecting agents, or by administering it in linkage to a homeobox- like peptide which is known to enter the nucleus (see e.g., Joliot et al., Proc. Natl. Acad. Sci. USA 88:1864-1868

(1991)), etc. Alternatively, a nucleic acid can be introduced intracellularly and incorporated within host cell DNA for expression, by homologous recombination.

The present invention also provides pharmaceutical compositions. Such compositions comprise a therapeutically effective amount of a compound, and a pharmaceutically acceptable carrier. In a specific embodiment, the term "pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly in humans. The term "carrier" refers to a diluent, adjuvant, excipient, or vehicle with which the therapeutic is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Water is a preferred carrier when the pharmaceutical composition is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid carriers, particularly for injectable solutions. Suitable pharmaceutical excipients include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. The composition, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents. These compositions can take the form of solutions, suspensions, emulsion, tablets, pills, capsules, powders, sustained-release formulations and the like. The composition can be formulated as a suppository, with traditional binders and carriers such as triglycerides. Oral formulation can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, Examples of suitable pharmaceutical carriers are described in "Remington's etc. Pharmaceutical Sciences" by E.W. Martin. Such compositions will contain a therapeutically effective amount of the compound, preferably in purified form, together with a suitable amount of carrier so as to provide the form for proper administration to the patient. The formulation should suit the mode of administration.

[421] In a preferred embodiment, the composition is formulated in accordance with routine procedures as a pharmaceutical composition adapted for intravenous administration to human beings. Typically, compositions for intravenous administration are solutions in sterile isotonic aqueous buffer. Where necessary, the composition may also include a solubilizing agent and a local anesthetic such as lignocaine to ease pain at the site of the

injection. Generally, the ingredients are supplied either separately or mixed together in unit dosage form, for example, as a dry lyophilized powder or water free concentrate in a hermetically sealed container such as an ampoule or sachette indicating the quantity of active agent. Where the composition is to be administered by infusion, it can be dispensed with an infusion bottle containing sterile pharmaceutical grade water or saline. Where the composition is administered by injection, an ampoule of sterile water for injection or saline can be provided so that the ingredients may be mixed prior to administration.

[422] The compounds of the invention can be formulated as neutral or salt forms. Pharmaceutically acceptable salts include those formed with anions such as those derived from hydrochloric, phosphoric, acetic, oxalic, tartaric acids, etc., and those formed with cations such as those derived from sodium, potassium, ammonium, calcium, ferric hydroxides, isopropylamine, triethylamine, 2-ethylamino ethanol, histidine, procaine, etc.

[423] The amount of the compound of the invention which will be effective in the treatment, inhibition and prevention of a disease or disorder associated with aberrant expression and/or activity of a polypeptide of the invention can be determined by standard clinical techniques. In addition, in vitro assays may optionally be employed to help identify optimal dosage ranges. The precise dose to be employed in the formulation will also depend on the route of administration, and the seriousness of the disease or disorder, and should be decided according to the judgment of the practitioner and each patient's circumstances. Effective doses may be extrapolated from dose-response curves derived from in vitro or animal model test systems.

[424] For antibodies, the dosage administered to a patient is typically 0.1 mg/kg to 100 mg/kg of the patient's body weight. Preferably, the dosage administered to a patient is between 0.1 mg/kg and 20 mg/kg of the patient's body weight, more preferably 1 mg/kg to 10 mg/kg of the patient's body weight. Generally, human antibodies have a longer half-life within the human body than antibodies from other species due to the immune response to the foreign polypeptides. Thus, lower dosages of human antibodies and less frequent administration is often possible. Further, the dosage and frequency of administration of antibodies of the invention may be reduced by enhancing uptake and tissue penetration (e.g., into the brain) of the antibodies by modifications such as, for example, lipidation.

[425] The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions of the invention. Optionally associated with such container(s) can be a notice in the form

prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration.

Diagnosis and Imaging

[426] Labeled antibodies, and derivatives and analogs thereof, which specifically bind to a polypeptide of interest can be used for diagnostic purposes to detect, diagnose, or monitor diseases, disorders, and/or conditions associated with the aberrant expression and/or activity of a polypeptide of the invention. The invention provides for the detection of aberrant expression of a polypeptide of interest, comprising (a) assaying the expression of the polypeptide of interest in cells or body fluid of an individual using one or more antibodies specific to the polypeptide interest and (b) comparing the level of gene expression with a standard gene expression level, whereby an increase or decrease in the assayed polypeptide gene expression level compared to the standard expression level is indicative of aberrant expression.

[427] The invention provides a diagnostic assay for diagnosing a disorder, comprising (a) assaying the expression of the polypeptide of interest in cells or body fluid of an individual using one or more antibodies specific to the polypeptide interest and (b) comparing the level of gene expression with a standard gene expression level, whereby an increase or decrease in the assayed polypeptide gene expression level compared to the standard expression level is indicative of a particular disorder. With respect to cancer, the presence of a relatively high amount of transcript in biopsied tissue from an individual may indicate a predisposition for the development of the disease, or may provide a means for detecting the disease prior to the appearance of actual clinical symptoms. A more definitive diagnosis of this type may allow health professionals to employ preventative measures or aggressive treatment earlier thereby preventing the development or further progression of the cancer.

[428] Antibodies of the invention can be used to assay protein levels in a biological sample using classical immunohistological methods known to those of skill in the art (e.g., see Jalkanen et al., J. Cell. Biol. 101:976-985 (1985); Jalkanen et al., J. Cell. Biol. 105:3087-3096 (1987)). Other antibody-based methods useful for detecting protein gene expression include immunoassays, such as the enzyme linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA). Suitable antibody assay labels are known in the

art and include enzyme labels, such as, glucose oxidase; radioisotopes, such as iodine (125I, 121I), carbon (14C), sulfur (35S), tritium (3H), indium (112In), and technetium (99Tc); luminescent labels, such as luminol; and fluorescent labels, such as fluorescein and rhodamine, and biotin.

[429] One facet of the invention is the detection and diagnosis of a disease or disorder associated with aberrant expression of a polypeptide of interest in an animal, preferably a mammal and most preferably a human. In one embodiment, diagnosis comprises: a) administering (for example, parenterally, subcutaneously, or intraperitoneally) to a subject an effective amount of a labeled molecule which specifically binds to the polypeptide of interest; b) waiting for a time interval following the administering for permitting the labeled molecule to preferentially concentrate at sites in the subject where the polypeptide is expressed (and for unbound labeled molecule to be cleared to background level); c) determining background level; and d) detecting the labeled molecule in the subject, such that detection of labeled molecule above the background level indicates that the subject has a particular disease or disorder associated with aberrant expression of the polypeptide of interest. Background level can be determined by various methods including, comparing the amount of labeled molecule detected to a standard value previously determined for a particular system.

[430] It will be understood in the art that the size of the subject and the imaging system used will determine the quantity of imaging moiety needed to produce diagnostic images. In the case of a radioisotope moiety, for a human subject, the quantity of radioactivity injected will normally range from about 5 to 20 millicuries of 99mTc. The labeled antibody or antibody fragment will then preferentially accumulate at the location of cells which contain the specific protein. *In vivo* tumor imaging is described in S.W. Burchiel et al., "Immunopharmacokinetics of Radiolabeled Antibodies and Their Fragments." (Chapter 13 in Tumor Imaging: The Radiochemical Detection of Cancer, S.W. Burchiel and B. A. Rhodes, eds., Masson Publishing Inc. (1982)).

[431] Depending on several variables, including the type of label used and the mode of administration, the time interval following the administration for permitting the labeled molecule to preferentially concentrate at sites in the subject and for unbound labeled molecule to be cleared to background level is 6 to 48 hours or 6 to 24 hours or 6 to 12 hours. In another embodiment the time interval following administration is 5 to 20 days or 5 to 10 days.

[432] In an embodiment, monitoring of the disease or disorder is carried out by repeating the method for diagnosing the disease or disease, for example, one month after initial diagnosis, six months after initial diagnosis, one year after initial diagnosis, etc.

Presence of the labeled molecule can be detected in the patient using methods known in the art for *in vivo* scanning. These methods depend upon the type of label used. Skilled artisans will be able to determine the appropriate method for detecting a particular label. Methods and devices that may be used in the diagnostic methods of the invention include, but are not limited to, computed tomography (CT), whole body scan such as position emission tomography (PET), magnetic resonance imaging (MRI), and sonography.

[434] In a specific embodiment, the molecule is labeled with a radioisotope and is detected in the patient using a radiation responsive surgical instrument (Thurston et al., U.S. Patent No. 5,441,050). In another embodiment, the molecule is labeled with a fluorescent compound and is detected in the patient using a fluorescence responsive scanning instrument. In another embodiment, the molecule is labeled with a positron emitting metal and is detected in the patent using positron emission-tomography. In yet another embodiment, the molecule is labeled with a paramagnetic label and is detected in a patient using magnetic resonance imaging (MRI).

Kits

[435] The present invention provides kits that can be used in the above methods. In one embodiment, a kit comprises an antibody of the invention, preferably a purified antibody, in one or more containers. In a specific embodiment, the kits of the present invention contain a substantially isolated polypeptide comprising an epitope which is specifically immunoreactive with an antibody included in the kit. Preferably, the kits of the present invention further comprise a control antibody which does not react with the polypeptide of interest. In another specific embodiment, the kits of the present invention contain a means for detecting the binding of an antibody to a polypeptide of interest (e.g., the antibody may be conjugated to a detectable substrate such as a fluorescent compound, an enzymatic substrate, a radioactive compound or a luminescent compound, or a second antibody which recognizes the first antibody may be conjugated to a detectable substrate).

[436] In another specific embodiment of the present invention, the kit is a diagnostic kit for use in screening serum containing antibodies specific against proliferative and/or cancerous polynucleotides and polypeptides. Such a kit may include a control antibody that

does not react with the polypeptide of interest. Such a kit may include a substantially isolated polypeptide antigen comprising an epitope which is specifically immunoreactive with at least one anti-polypeptide antigen antibody. Further, such a kit includes means for detecting the binding of said antibody to the antigen (e.g., the antibody may be conjugated to a fluorescent compound such as fluorescein or rhodamine which can be detected by flow cytometry). In specific embodiments, the kit may include a recombinantly produced or chemically synthesized polypeptide antigen. The polypeptide antigen of the kit may also be attached to a solid support.

[437] In a more specific embodiment the detecting means of the above-described kit includes a solid support to which said polypeptide antigen is attached. Such a kit may also include a non-attached reporter-labeled anti-human antibody. In this embodiment, binding of the antibody to the polypeptide antigen can be detected by binding of the said reporter-labeled antibody.

[438] In an additional embodiment, the invention includes a diagnostic kit for use in screening serum containing antigens of the polypeptide of the invention. The diagnostic kit includes a substantially isolated antibody specifically immunoreactive with polypeptide or polypucleotide antigens, and means for detecting the binding of the polypucleotide or polypeptide antigen to the antibody. In one embodiment, the antibody is attached to a solid support. In a specific embodiment, the antibody may be a monoclonal antibody. The detecting means of the kit may include a second, labeled monoclonal antibody. Alternatively, or in addition, the detecting means may include a labeled, competing antigen.

[439] In one diagnostic configuration, test serum is reacted with a solid phase reagent having a surface-bound antigen obtained by the methods of the present invention. After binding with specific antigen antibody to the reagent and removing unbound serum components by washing, the reagent is reacted with reporter-labeled anti-human antibody to bind reporter to the reagent in proportion to the amount of bound anti-antigen antibody on the solid support. The reagent is again washed to remove unbound labeled antibody, and the amount of reporter associated with the reagent is determined. Typically, the reporter is an enzyme which is detected by incubating the solid phase in the presence of a suitable fluorometric, luminescent or colorimetric substrate (Sigma, St. Louis, MO).

[440] The solid surface reagent in the above assay is prepared by known techniques for attaching protein material to solid support material, such as polymeric beads, dip sticks, 96-well plate or filter material. These attachment methods generally include non-specific

adsorption of the protein to the support or covalent attachment of the protein, typically through a free amine group, to a chemically reactive group on the solid support, such as an activated carboxyl, hydroxyl, or aldehyde group. Alternatively, streptavidin coated plates can be used in conjunction with biotinylated antigen(s).

[441] Thus, the invention provides an assay system or kit for carrying out this diagnostic method. The kit generally includes a support with surface-bound recombinant antigens, and a reporter-labeled anti-human antibody for detecting surface-bound anti-antigen antibody.

Uses of the Polynucleotides

[442] Each of the polynucleotides identified herein can be used in numerous ways as reagents. The following description should be considered exemplary and utilizes known techniques.

[443] The polynucleotides of the present invention are useful for chromosome identification. There exists an ongoing need to identify new chromosome markers, since few chromosome marking reagents, based on actual sequence data (repeat polymorphisms), are presently available. Each sequence is specifically targeted to and can hybridize with a particular location on an individual human chromosome, thus each polynucleotide of the present invention can routinely be used as a chromosome marker using techniques known in the art. Table 1B, column 9 provides the chromosome location of some of the polynucleotides of the invention.

[444] Briefly, sequences can be mapped to chromosomes by preparing PCR primers (preferably at least 15 bp (e.g., 15-25 bp) from the sequences shown in SEQ ID NO:X. Primers can optionally be selected using computer analysis so that primers do not span more than one predicted exon in the genomic DNA. These primers are then used for PCR screening of somatic cell hybrids containing individual human chromosomes. Only those hybrids containing the human gene corresponding to SEQ ID NO:X will yield an amplified fragment.

[445] Similarly, somatic hybrids provide a rapid method of PCR mapping the polynucleotides to particular chromosomes. Three or more clones can be assigned per day using a single thermal cycler. Moreover, sublocalization of the polynucleotides can be achieved with panels of specific chromosome fragments. Other gene mapping strategies

that can be used include in situ hybridization, prescreening with labeled flow-sorted chromosomes, preselection by hybridization to construct chromosome specific-cDNA libraries, and computer mapping techniques (See, e.g., Shuler, Trends Biotechnol 16:456-459 (1998) which is hereby incorporated by reference in its entirety).

[446] Precise chromosomal location of the polynucleotides can also be achieved using fluorescence in situ hybridization (FISH) of a metaphase chromosomal spread. This technique uses polynucleotides as short as 500 or 600 bases; however, polynucleotides 2,000-4,000 bp are preferred. For a review of this technique, see Verma et al., "Human Chromosomes: a Manual of Basic Techniques," Pergamon Press, New York (1988).

[447] For chromosome mapping, the polynucleotides can be used individually (to mark a single chromosome or a single site on that chromosome) or in panels (for marking multiple sites and/or multiple chromosomes).

[448] Thus, the present invention also provides a method for chromosomal localization which involves (a) preparing PCR primers from the polynucleotide sequences in Table 1B and/or Table 2 and SEQ ID NO:X and (b) screening somatic cell hybrids containing individual chromosomes.

The polynucleotides of the present invention would likewise be useful for radiation hybrid mapping, HAPPY mapping, and long range restriction mapping. For a review of these techniques and others known in the art, see, e.g. Dear, "Genome Mapping: A Practical Approach," IRL Press at Oxford University Press, London (1997); Aydin, J. Mol. Med. 77:691-694 (1999); Hacia et al., Mol. Psychiatry 3:483-492 (1998); Herrick et al., Chromosome Res. 7:409-423 (1999); Hamilton et al., Methods Cell Biol. 62:265-280 (2000); and/or Ott, J. Hered. 90:68-70 (1999) each of which is hereby incorporated by reference in its entirety.

[450] Once a polynucleotide has been mapped to a precise chromosomal location, the physical position of the polynucleotide can be used in linkage analysis. Linkage analysis establishes coinheritance between a chromosomal location and presentation of a particular disease. (Disease mapping data are found, for example, in V. McKusick, Mendelian Inheritance in Man (available on line through Johns Hopkins University Welch Medical Library)). Column 10 of Table 1B provides an OMIM reference identification number of diseases associated with the cytologic band disclosed in column 9 of Table 1B, as determined using techniques described herein and by reference to Table 5. Assuming 1 megabase mapping resolution and one gene per 20 kb, a cDNA precisely localized to a

chromosomal region associated with the disease could be one of 50-500 potential causative genes.

[451] Thus, once coinheritance is established, differences in a polynucleotide of the invention and the corresponding gene between affected and unaffected individuals can be examined. First, visible structural alterations in the chromosomes, such as deletions or translocations, are examined in chromosome spreads or by PCR. If no structural alterations exist, the presence of point mutations are ascertained. Mutations observed in some or all affected individuals, but not in normal individuals, indicates that the mutation may cause the disease. However, complete sequencing of the polypeptide and the corresponding gene from several normal individuals is required to distinguish the mutation from a polymorphism. If a new polymorphism is identified, this polymorphic polypeptide can be used for further linkage analysis.

[452] Furthermore, increased or decreased expression of the gene in affected individuals as compared to unaffected individuals can be assessed using the polynucleotides of the invention. Any of these alterations (altered expression, chromosomal rearrangement, or mutation) can be used as a diagnostic or prognostic marker. Diagnostic and prognostic methods, kits and reagents encompassed by the present invention are briefly described below and more thoroughly elsewhere herein (see e.g., the sections labeled "Antibodies", "Diagnostic Assays", and "Methods for Detecting Diseases").

[453] Thus, the invention also provides a diagnostic method useful during diagnosis of a disorder, involving measuring the expression level of polynucleotides of the present invention in cells or body fluid from an individual and comparing the measured gene expression level with a standard level of polynucleotide expression level, whereby an increase or decrease in the gene expression level compared to the standard is indicative of a disorder. Additional non-limiting examples of diagnostic methods encompassed by the present invention are more thoroughly described elsewhere herein (see, e.g., Example 12).

[454] In still another embodiment, the invention includes a kit for analyzing samples for the presence of proliferative and/or cancerous polynucleotides derived from a test subject. In a general embodiment, the kit includes at least one polynucleotide probe containing a nucleotide sequence that will specifically hybridize with a polynucleotide of the invention and a suitable container. In a specific embodiment, the kit includes two polynucleotide probes defining an internal region of the polynucleotide of the invention, where each probe has one strand containing a 31'mer-end internal to the region. In a further

embodiment, the probes may be useful as primers for polymerase chain reaction amplification.

[455] Where a diagnosis of a related disorder, including, for example, diagnosis of a tumor, has already been made according to conventional methods, the present invention is useful as a prognostic indicator, whereby patients exhibiting enhanced or depressed polynucleotide of the invention expression will experience a worse clinical outcome relative to patients expressing the gene at a level nearer the standard level.

[456] By "measuring the expression level of polynucleotides of the invention" is intended qualitatively or quantitatively measuring or estimating the level of the polypeptide of the invention or the level of the mRNA encoding the polypeptide of the invention in a first biological sample either directly (e.g., by determining or estimating absolute protein level or mRNA level) or relatively (e.g., by comparing to the polypeptide level or mRNA level in a second biological sample). Preferably, the polypeptide level or mRNA level in the first biological sample is measured or estimated and compared to a standard polypeptide level or mRNA level, the standard being taken from a second biological sample obtained from an individual not having the related disorder or being determined by averaging levels from a population of individuals not having a related disorder. As will be appreciated in the art, once a standard polypeptide level or mRNA level is known, it can be used repeatedly as a standard for comparison.

[457] By "biological sample" is intended any biological sample obtained from an individual, body fluid, cell line, tissue culture, or other source which contains polypeptide of the present invention or the corresponding mRNA. As indicated, biological samples include body fluids (such as semen, lymph, vaginal pool, sera, plasma, urine, synovial fluid and spinal fluid) which contain the polypeptide of the present invention, and tissue sources found to express the polypeptide of the present invention. Methods for obtaining tissue biopsies and body fluids from mammals are well known in the art. Where the biological sample is to include mRNA, a tissue biopsy is the preferred source.

[458] The method(s) provided above may preferably be applied in a diagnostic method and/or kits in which polynucleotides and/or polypeptides of the invention are attached to a solid support. In one exemplary method, the support may be a "gene chip" or a "biological chip" as described in US Patents 5,837,832, 5,874,219, and 5,856,174. Further, such a gene chip with polynucleotides of the invention attached may be used to identify polymorphisms between the isolated polynucleotide sequences of the invention, with polynucleotides

isolated from a test subject. The knowledge of such polymorphisms (i.e. their location, as well as, their existence) would be beneficial in identifying disease loci for many disorders, such as for example, in neural disorders, immune system disorders, muscular disorders, reproductive disorders, gastrointestinal disorders, pulmonary disorders, digestive disorders, metabolic disorders, cardiovascular disorders, renal disorders, proliferative disorders, and/or cancerous diseases and conditions. Such a method is described in US Patents 5,858,659 and 5,856,104. The US Patents referenced *supra* are hereby incorporated by reference in their entirety herein.

[459] The present invention encompasses polynucleotides of the present invention that are chemically synthesized, or reproduced as peptide nucleic acids (PNA), or according to other methods known in the art. The use of PNAs would serve as the preferred form if the polynucleotides of the invention are incorporated onto a solid support, or gene chip. For the purposes of the present invention, a peptide nucleic acid (PNA) is a polyamide type of DNA analog and the monomeric units for adenine, guanine, thymine and cytosine are available commercially (Perceptive Biosystems). Certain components of DNA, such as phosphorus, phosphorus oxides, or deoxyribose derivatives, are not present in PNAs. As disclosed by Nielsen et al., Science 254, 1497 (1991); and Egholm et al., Nature 365, 666 (1993), PNAs bind specifically and tightly to complementary DNA strands and are not degraded by nucleases. In fact, PNA binds more strongly to DNA than DNA itself does. This is probably because there is no electrostatic repulsion between the two strands, and also the polyamide backbone is more flexible. Because of this, PNA/DNA duplexes bind under a wider range of stringency conditions than DNA/DNA duplexes, making it easier to perform multiplex hybridization. Smaller probes can be used than with DNA due to the strong binding. In addition, it is more likely that single base mismatches can be determined with PNA/DNA hybridization because a single mismatch in a PNA/DNA 15-mer lowers the melting point (T.sub.m) by 8°-20° C, vs. 4°-16° C for the DNA/DNA 15-mer duplex. Also, the absence of charge groups in PNA means that hybridization can be done at low ionic strengths and reduce possible interference by salt during the analysis.

[460] The compounds of the present invention have uses which include, but are not limited to, detecting cancer in mammals. In particular the invention is useful during diagnosis of pathological cell proliferative neoplasias which include, but are not limited to: acute myelogenous leukemias including acute monocytic leukemia, acute myeloblastic leukemia, acute promyelocytic leukemia, acute myelomonocytic leukemia, acute

erythroleukemia, acute megakaryocytic leukemia, and acute undifferentiated leukemia, etc.; and chronic myelogenous leukemias including chronic myelomonocytic leukemia, chronic granulocytic leukemia, etc. Preferred mammals include monkeys, apes, cats, dogs, cows, pigs, horses, rabbits and humans. Particularly preferred are humans.

[461] Pathological cell proliferative disorders are often associated with inappropriate activation of proto-oncogenes. (Gelmann, E. P. et al., "The Etiology of Acute Leukemia: Molecular Genetics and Viral Oncology," in Neoplastic Diseases of the Blood, Vol 1., Wiernik, P. H. et al. eds., 161-182 (1985)). Neoplasias are now believed to result from the qualitative alteration of a normal cellular gene product, or from the quantitative modification of gene expression by insertion into the chromosome of a viral sequence, by chromosomal translocation of a gene to a more actively transcribed region, or by some other mechanism. (Gelmann et al., *supra*) It is likely that mutated or altered expression of specific genes is involved in the pathogenesis of some leukemias, among other tissues and cell types. (Gelmann et al., *supra*) Indeed, the human counterparts of the oncogenes involved in some animal neoplasias have been amplified or translocated in some cases of human leukemia and carcinoma. (Gelmann et al., *supra*)

[462] For example, c-myc expression is highly amplified in the non-lymphocytic leukemia cell line HL-60. When HL-60 cells are chemically induced to stop proliferation, the level of c-myc is found to be downregulated. (International Publication Number WO 91/15580). However, it has been shown that exposure of HL-60 cells to a DNA construct that is complementary to the 5' end of c-myc or c-myb blocks translation of the corresponding mRNAs which downregulates expression of the c-myc or c-myb proteins and causes arrest of cell proliferation and differentiation of the treated cells. (International Publication Number WO 91/15580; Wickstrom et al., Proc. Natl. Acad. Sci. 85:1028 (1988); Anfossi et al., Proc. Natl. Acad. Sci. 86:3379 (1989)). However, the skilled artisan would appreciate the present invention's usefulness is not be limited to treatment, prevention, and/or prognosis of proliferative disorders of cells and tissues of hematopoietic origin, in light of the numerous cells and cell types of varying origins which are known to exhibit proliferative phenotypes.

[463] In addition to the foregoing, a polynucleotide of the present invention can be used to control gene expression through triple helix formation or through antisense DNA or RNA. Antisense techniques are discussed, for example, in Okano, J. Neurochem. 56: 560 (1991); "Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression, CRC Press,

Boca Raton, FL (1988). Triple helix formation is discussed in, for instance Lee et al., Nucleic Acids Research 6: 3073 (1979); Cooney et al., Science 241: 456 (1988); and Dervan et al., Science 251: 1360 (1991). Both methods rely on binding of the polynucleotide to a complementary DNA or RNA. For these techniques, preferred polynucleotides are usually oligonucleotides 20 to 40 bases in length and complementary to either the region of the gene involved in transcription (triple helix - see Lee et al., Nucl. Acids Res. 6:3073 (1979); Cooney et al., Science 241:456 (1988); and Dervan et al., Science 251:1360 (1991)) or to the mRNA itself (antisense - Okano, J. Neurochem. 56:560 (1991); Oligodeoxy-nucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988)). Triple helix formation optimally results in a shut-off of RNA transcription from DNA, while antisense RNA hybridization blocks translation of an mRNA molecule into polypeptide. The oligonucleotide described above can also be delivered to cells such that the antisense RNA or DNA may be expressed in vivo to inhibit production of polypeptide of the present invention antigens. Both techniques are effective in model systems, and the information disclosed herein can be used to design antisense or triple helix polynucleotides in an effort to treat disease, and in particular, for the treatment of proliferative diseases and/or conditions. Non-limiting antisense and triple helix methods encompassed by the present invention are more thoroughly described elsewhere herein (see, e.g., the section labeled "Antisense and Ribozyme (Antagonists)").

[464] Polynucleotides of the present invention are also useful in gene therapy. One goal of gene therapy is to insert a normal gene into an organism having a defective gene, in an effort to correct the genetic defect. The polynucleotides disclosed in the present invention offer a means of targeting such genetic defects in a highly accurate manner. Another goal is to insert a new gene that was not present in the host genome, thereby producing a new trait in the host cell. Additional non-limiting examples of gene therapy methods encompassed by the present invention are more thoroughly described elsewhere herein (see, e.g., the sections labeled "Gene Therapy Methods", and Examples 16, 17 and 18).

[465] The polynucleotides are also useful for identifying individuals from minute biological samples. The United States military, for example, is considering the use of restriction fragment length polymorphism (RFLP) for identification of its personnel. In this technique, an individual's genomic DNA is digested with one or more restriction enzymes, and probed on a Southern blot to yield unique bands for identifying personnel. This

method does not suffer from the current limitations of "Dog Tags" which can be lost, switched, or stolen, making positive identification difficult. The polynucleotides of the present invention can be used as additional DNA markers for RFLP.

[466] The polynucleotides of the present invention can also be used as an alternative to RFLP, by determining the actual base-by-base DNA sequence of selected portions of an individual's genome. These sequences can be used to prepare PCR primers for amplifying and isolating such selected DNA, which can then be sequenced. Using this technique, individuals can be identified because each individual will have a unique set of DNA sequences. Once an unique ID database is established for an individual, positive identification of that individual, living or dead, can be made from extremely small tissue samples.

Forensic biology also benefits from using DNA-based identification techniques as disclosed herein. DNA sequences taken from very small biological samples such as tissues, e.g., hair or skin, or body fluids, e.g., blood, saliva, semen, synovial fluid, amniotic fluid, breast milk, lymph, pulmonary sputum or surfactant, urine, fecal matter, etc., can be amplified using PCR. In one prior art technique, gene sequences amplified from polymorphic loci, such as DQa class II HLA gene, are used in forensic biology to identify individuals. (Erlich, H., PCR Technology, Freeman and Co. (1992)). Once these specific polymorphic loci are amplified, they are digested with one or more restriction enzymes, yielding an identifying set of bands on a Southern blot probed with DNA corresponding to the DQa class II HLA gene. Similarly, polynucleotides of the present invention can be used as polymorphic markers for forensic purposes.

[468] There is also a need for reagents capable of identifying the source of a particular tissue. Such need arises, for example, in forensics when presented with tissue of unknown origin. Appropriate reagents can comprise, for example, DNA probes or primers prepared from the sequences of the present invention, specific to tissues, including but not limited to those shown in Table 1B. Panels of such reagents can identify tissue by species and/or by organ type. In a similar fashion, these reagents can be used to screen tissue cultures for contamination. Additional non-limiting examples of such uses are further described herein.

[469] The polynucleotides of the present invention are also useful as hybridization probes for differential identification of the tissue(s) or cell type(s) present in a biological sample. Similarly, polypeptides and antibodies directed to polypeptides of the present invention are useful to provide immunological probes for differential identification of the

tissue(s) (e.g., immunohistochemistry assays) or cell type(s) (e.g., immunocytochemistry assays). In addition, for a number of disorders of the above tissues or cells, significantly higher or lower levels of gene expression of the polynucleotides/polypeptides of the present invention may be detected in certain tissues (e.g., tissues expressing polypeptides and/or polynucleotides of the present invention, for example, those disclosed in column 8 of Table 1B, and/or cancerous and/or wounded tissues) or bodily fluids (e.g., semen, lymph, vaginal pool, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to a "standard" gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

[470] Thus, the invention provides a diagnostic method of a disorder, which involves: (a) assaying gene expression level in cells or body fluid of an individual; (b) comparing the gene expression level with a standard gene expression level, whereby an increase or decrease in the assayed gene expression level compared to the standard expression level is indicative of a disorder.

[471] In the very least, the polynucleotides of the present invention can be used as molecular weight markers on Southern gels, as diagnostic probes for the presence of a specific mRNA in a particular cell type, as a probe to "subtract-out" known sequences in the process of discovering novel polynucleotides, for selecting and making oligomers for attachment to a "gene chip" or other support, to raise anti-DNA antibodies using DNA immunization techniques, and as an antigen to elicit an immune response.

Uses of the Polypeptides

[472] Each of the polypeptides identified herein can be used in numerous ways. The following description should be considered exemplary and utilizes known techniques.

[473] Polypeptides and antibodies directed to polypeptides of the present invention are useful to provide immunological probes for differential identification of the tissue(s) (e.g., immunohistochemistry assays such as, for example, ABC immunoperoxidase (Hsu et al., J. Histochem. Cytochem. 29:577-580 (1981)) or cell type(s) (e.g., immunocytochemistry assays).

[474] Antibodies can be used to assay levels of polypeptides encoded by polynucleotides of the invention in a biological sample using classical immunohistological methods known to those of skill in the art (e.g., see Jalkanen, et al., J. Cell. Biol. 101:976-985 (1985); Jalkanen, et al., J. Cell. Biol. 105:3087-3096 (1987)). Other antibody-based

methods useful for detecting protein gene expression include immunoassays, such as the enzyme linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA). Suitable antibody assay labels are known in the art and include enzyme labels, such as, glucose oxidase; radioisotopes, such as iodine (¹³¹I, ¹²⁵I, ¹²³I, ¹²¹I), carbon (¹⁴C), sulfur (³⁵S), tritium (³H), indium (^{115m}In, ^{113m}In, ¹¹²In, ¹¹¹In), and technetium (⁹⁹Tc, ^{99m}Tc), thallium (²⁰¹Ti), gallium (⁶⁸Ga, ⁶⁷Ga), palladium (¹⁰³Pd), molybdenum (⁹⁹Mo), xenon (¹³³Xe), fluorine (¹⁸F), ¹⁵³Sm, ¹⁷⁷Lu, ¹⁵⁹Gd, ¹⁴⁹Pm, ¹⁴⁰La, ¹⁷⁵Yb, ¹⁶⁶Ho, ⁹⁰Y, ⁴⁷Sc, ¹⁸⁶Re, ¹⁸⁸Re, ¹⁴²Pr, ¹⁰⁵Rh, ⁹⁷Ru; luminescent labels, such as luminol; and fluorescent labels, such as fluorescein and rhodamine, and biotin.

[475] In addition to assaying levels of polypeptide of the present invention in a biological sample, proteins can also be detected *in vivo* by imaging. Antibody labels or markers for *in vivo* imaging of protein include those detectable by X-radiography, NMR or ESR. For X-radiography, suitable labels include radioisotopes such as barium or cesium, which emit detectable radiation but are not overtly harmful to the subject. Suitable markers for NMR and ESR include those with a detectable characteristic spin, such as deuterium, which may be incorporated into the antibody by labeling of nutrients for the relevant hybridoma.

A protein-specific antibody or antibody fragment which has been labeled with an [476] appropriate detectable imaging moiety, such as a radioisotope (for example, ¹³¹I, ¹¹²In, ^{99m}Tc, (¹³¹I, ¹²⁵I, ¹²³I, ¹²¹I), carbon (¹⁴C), sulfur (³⁵S), tritium (³H), indium (^{115m}In, ^{113m}In, ¹¹²In, ¹¹¹In), and technetium (⁹⁹Tc, ^{99m}Tc), thallium (²⁰¹Ti), gallium (⁶⁸Ga, ⁶⁷Ga), palladium (103Pd), molybdenum (99Mo), xenon (133Xe), fluorine (18F, 153Sm, 177Lu, 159Gd, 149Pm, 140La, ¹⁷⁵Yb, ¹⁶⁶Ho, ⁹⁰Y, ⁴⁷Sc, ¹⁸⁶Re, ¹⁸⁸Re, ¹⁴²Pr, ¹⁰⁵Rh, ⁹⁷Ru), a radio-opaque substance, or a material detectable by nuclear magnetic resonance, is introduced (for example, parenterally, subcutaneously or intraperitoneally) into the mammal to be examined for immune system disorder. It will be understood in the art that the size of the subject and the imaging system used will determine the quantity of imaging moiety needed to produce diagnostic images. In the case of a radioisotope moiety, for a human subject, the quantity of radioactivity injected will normally range from about 5 to 20 millicuries of 99mTc. The labeled antibody or antibody fragment will then preferentially accumulate at the location of cells which express the polypeptide encoded by a polynucleotide of the invention. In vivo tumor imaging is described in S.W. Burchiel et al., "Immunopharmacokinetics of Radiolabeled Antibodies and Their Fragments" (Chapter 13 in Tumor Imaging: The Radiochemical

Detection of Cancer, S.W. Burchiel and B. A. Rhodes, eds., Masson Publishing Inc. (1982)).

In one embodiment, the invention provides a method for the specific delivery of compositions of the invention to cells by administering polypeptides of the invention (e.g., polypeptides encoded by polynucleotides of the invention and/or antibodies) that are associated with heterologous polypeptides or nucleic acids. In one example, the invention provides a method for delivering a therapeutic protein into the targeted cell. In another example, the invention provides a method for delivering a single stranded nucleic acid (e.g., antisense or ribozymes) or double stranded nucleic acid (e.g., DNA that can integrate into the cell's genome or replicate episomally and that can be transcribed) into the targeted cell.

[478] In another embodiment, the invention provides a method for the specific destruction of cells (e.g., the destruction of tumor cells) by administering polypeptides of the invention in association with toxins or cytotoxic prodrugs.

[479] By "toxin" is meant one or more compounds that bind and activate endogenous cytotoxic effector systems, radioisotopes, holotoxins, modified toxins, catalytic subunits of toxins, or any molecules or enzymes not normally present in or on the surface of a cell that under defined conditions cause the cell's death. Toxins that may be used according to the methods of the invention include, but are not limited to, radioisotopes known in the art, compounds such as, for example, antibodies (or complement fixing containing portions thereof) that bind an inherent or induced endogenous cytotoxic effector system, thymidine kinase, endonuclease, RNAse, alpha toxin, ricin, abrin, Pseudomonas exotoxin A, diphtheria toxin, saporin, momordin, gelonin, pokeweed antiviral protein, alpha-sarcin and cholera toxin. "Toxin" also includes a cytostatic or cytocidal agent, a therapeutic agent or a radioactive metal ion, e.g., alpha-emitters such as, for example, ²¹³Bi, or other radioisotopes such as, for example, ¹⁰³Pd, ¹³³Xe, ¹³¹I, ⁶⁸Ge, ⁵⁷Co, ⁶⁵Zn, ⁸⁵Sr, ³²P, ³⁵S, ⁹⁰Y, ¹⁵³Sm, ¹⁵³Gd, ¹⁶⁹Yb, ⁵¹Cr, ⁵⁴Mn, ⁷⁵Se, ¹¹³Sn, ⁹⁰Yttrium, ¹¹⁷Tin, ¹⁸⁶Rhenium, ¹⁶⁶Holmium, and ¹⁸⁸Rhenium; luminescent labels, such as luminol; and fluorescent labels, such as fluorescein and rhodamine, and biotin. In a specific embodiment, the invention provides a method for the specific destruction of cells (e.g., the destruction of tumor cells) by administering polypeptides of the invention or antibodies of the invention in association with the radioisotope ⁹⁰Y. In another specific embodiment, the invention provides a method for the specific destruction of cells (e.g., the destruction of tumor cells) by administering polypeptides of the invention or antibodies of the invention in association with the radioisotope ¹¹¹In. In a further specific embodiment, the invention provides a method for the specific destruction of cells (e.g., the destruction of tumor cells) by administering polypeptides of the invention or antibodies of the invention in association with the radioisotope ¹³¹I.

[480] Techniques known in the art may be applied to label polypeptides of the invention (including antibodies). Such techniques include, but are not limited to, the use of bifunctional conjugating agents (see e.g., U.S. Patent Nos. 5,756,065; 5,714,631; 5,696,239; 5,652,361; 5,505,931; 5,489,425; 5,435,990; 5,428,139; 5,342,604; 5,274,119; 4,994,560; and 5,808,003; the contents of each of which are hereby incorporated by reference in its entirety).

[481] Thus, the invention provides a diagnostic method of a disorder, which involves (a) assaying the expression level of a polypeptide of the present invention in cells or body fluid of an individual; and (b) comparing the assayed polypeptide expression level with a standard polypeptide expression level, whereby an increase or decrease in the assayed polypeptide expression level compared to the standard expression level is indicative of a disorder. With respect to cancer, the presence of a relatively high amount of transcript in biopsied tissue from an individual may indicate a predisposition for the development of the disease, or may provide a means for detecting the disease prior to the appearance of actual clinical symptoms. A more definitive diagnosis of this type may allow health professionals to employ preventative measures or aggressive treatment earlier thereby preventing the development or further progression of the cancer.

[482] Moreover, polypeptides of the present invention can be used to treat or prevent diseases or conditions such as, for example, neural disorders, immune system disorders, muscular disorders, reproductive disorders, gastrointestinal disorders, pulmonary disorders, cardiovascular disorders, renal disorders, proliferative disorders, and/or cancerous diseases and conditions. For example, patients can be administered a polypeptide of the present invention in an effort to replace absent or decreased levels of the polypeptide (e.g., insulin), to supplement absent or decreased levels of a different polypeptide (e.g., hemoglobin S for hemoglobin B, SOD, catalase, DNA repair proteins), to inhibit the activity of a polypeptide (e.g., an oncogene or tumor supressor), to activate the activity of a polypeptide (e.g., by binding to a receptor), to reduce the activity of a membrane bound receptor by competing with it for free ligand (e.g., soluble TNF receptors used in reducing inflammation), or to

bring about a desired response (e.g., blood vessel growth inhibition, enhancement of the immune response to proliferative cells or tissues).

[483] Similarly, antibodies directed to a polypeptide of the present invention can also be used to treat disease (as described *supra*, and elsewhere herein). For example, administration of an antibody directed to a polypeptide of the present invention can bind, and/or neutralize the polypeptide, and/or reduce overproduction of the polypeptide. Similarly, administration of an antibody can activate the polypeptide, such as by binding to a polypeptide bound to a membrane (receptor).

[484] At the very least, the polypeptides of the present invention can be used as molecular weight markers on SDS-PAGE gels or on molecular sieve gel filtration columns using methods well known to those of skill in the art. Polypeptides can also be used to raise antibodies, which in turn are used to measure protein expression from a recombinant cell, as a way of assessing transformation of the host cell. Moreover, the polypeptides of the present invention can be used to test the biological activities described herein.

Diagnostic Assays

[485] The compounds of the present invention are useful for diagnosis, treatment, prevention and/or prognosis of various disorders in mammals, preferably humans. Such disorders include, but are not limited to, those described in the "Preferred Indications" column in Table 1D and Table 1E, and also as described herein under the section heading "Biological Activities".

[486] For a number of disorders, substantially altered (increased or decreased) levels of gene expression can be detected in tissues, cells or bodily fluids (e.g., sera, plasma, urine, semen, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to a "standard" gene expression level, that is, the expression level in tissues or bodily fluids from an individual not having the disorder. Thus, the invention provides a diagnostic method useful during diagnosis of a disorder, which involves measuring the expression level of the gene encoding the polypeptide in tissues, cells or body fluid from an individual and comparing the measured gene expression level with a standard gene expression level, whereby an increase or decrease in the gene expression level(s) compared to the standard is indicative of a disorder. These diagnostic assays may be performed *in vivo* or *in vitro*, such as, for example, on blood samples, biopsy tissue or autopsy tissue.

[487] The present invention is also useful as a prognostic indicator, whereby patients

exhibiting enhanced or depressed gene expression will experience a worse clinical outcome relative to patients expressing the gene at a level nearer the standard level.

[488] In certain embodiments, a polypeptide of the invention, or polynucleotides, antibodies, agonists, or antagonists corresponding to that polypeptide, may be used to diagnose and/or prognose diseases and/or disorders associated with the tissue(s) in which the polypeptide of the invention is expressed, including one, two, three, four, five, or more tissues disclosed in Table 1B, column 8 (Tissue Distribution Library Code).

[489] By "assaying the expression level of the gene encoding the polypeptide" is intended qualitatively or quantitatively measuring or estimating the level of the polypeptide of the invention or the level of the mRNA encoding the polypeptide of the invention in a first biological sample either directly (e.g., by determining or estimating absolute protein level or mRNA level) or relatively (e.g., by comparing to the polypeptide level or mRNA level in a second biological sample). Preferably, the polypeptide expression level or mRNA level in the first biological sample is measured or estimated and compared to a standard polypeptide level or mRNA level, the standard being taken from a second biological sample obtained from an individual not having the disorder or being determined by averaging levels from a population of individuals not having the disorder. As will be appreciated in the art, once a standard polypeptide level or mRNA level is known, it can be used repeatedly as a standard for comparison.

[490] By "biological sample" is intended any biological sample obtained from an individual, cell line, tissue culture, or other source containing polypeptides of the invention (including portions thereof) or mRNA. As indicated, biological samples include body fluids (such as sera, plasma, urine, synovial fluid and spinal fluid) and tissue sources found to express the full length or fragments thereof of a polypeptide or mRNA. Methods for obtaining tissue biopsies and body fluids from mammals are well known in the art. Where the biological sample is to include mRNA, a tissue biopsy is the preferred source.

[491] Total cellular RNA can be isolated from a biological sample using any suitable technique such as the single-step guanidinium-thiocyanate-phenol-chloroform method described in Chomczynski and Sacchi, Anal. Biochem. 162:156-159 (1987). Levels of mRNA encoding the polypeptides of the invention are then assayed using any appropriate method. These include Northern blot analysis, S1 nuclease mapping, the polymerase chain reaction (PCR), reverse transcription in combination with the polymerase chain reaction (RT-PCR), and reverse transcription in combination with the ligase chain reaction

(RT-LCR).

[492] The present invention also relates to diagnostic assays such as quantitative and diagnostic assays for detecting levels of polypeptides of the invention, in a biological sample (e.g., cells and tissues), including determination of normal and abnormal levels of polypeptides. Thus, for instance, a diagnostic assay in accordance with the invention for detecting over-expression of polypeptides of the invention compared to normal control tissue samples may be used to detect the presence of tumors. Assay techniques that can be used to determine levels of a polypeptide, such as a polypeptide of the present invention in a sample derived from a host are well-known to those of skill in the art. Such assay methods include radioimmunoassays, competitive-binding assays, Western Blot analysis and ELISA assays. Assaying polypeptide levels in a biological sample can occur using any art-known method.

[493] Assaying polypeptide levels in a biological sample can occur using antibody-based techniques. For example, polypeptide expression in tissues can be studied with classical immunohistological methods (Jalkanen et al., J. Cell. Biol. 101:976-985 (1985); Jalkanen, M., et al., J. Cell . Biol. 105:3087-3096 (1987)). Other antibody-based methods useful for detecting polypeptide gene expression include immunoassays, such as the enzyme linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA). Suitable antibody assay labels are known in the art and include enzyme labels, such as, glucose oxidase, and radioisotopes, such as iodine (125 I, 121 I), carbon (14 C), sulfur (35 S), tritium (3H), indium (112 In), and technetium (99m Tc), and fluorescent labels, such as fluorescein and rhodamine, and biotin.

[494] The tissue or cell type to be analyzed will generally include those which are known, or suspected, to express the gene of inteest (such as, for example, cancer). The protein isolation methods employed herein may, for example, be such as those described in Harlow and Lane (Harlow, E. and Lane, D., 1988, "Antibodies: A Laboratory Manual", Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York), which is incorporated herein by reference in its entirety. The isolated cells can be derived from cell culture or from a patient. The analysis of cells taken from culture may be a necessary step in the assessment of cells that could be used as part of a cell-based gene therapy technique or, alternatively, to test the effect of compounds on the expression of the gene.

[495] For example, antibodies, or fragments of antibodies, such as those described herein, may be used to quantitatively or qualitatively detect the presence of gene products

or conserved variants or peptide fragments thereof. This can be accomplished, for example, by immunofluorescence techniques employing a fluorescently labeled antibody coupled with light microscopic, flow cytometric, or fluorimetric detection.

[496] In a preferred embodiment, antibodies, or fragments of antibodies directed to any one or all of the predicted epitope domains of the polypeptides of the invention (shown in column 7 of Table 1B) may be used to quantitatively or qualitatively detect the presence of gene products or conserved variants or peptide fragments thereof. This can be accomplished, for example, by immunofluorescence techniques employing a fluorescently labeled antibody coupled with light microscopic, flow cytometric, or fluorimetric detection.

[497] In an additional preferred embodiment, antibodies, or fragments of antibodies directed to a conformational epitope of a polypeptide of the invention may be used to quantitatively or qualitatively detect the presence of gene products or conserved variants or peptide fragments thereof. This can be accomplished, for example, by immunofluorescence techniques employing a fluorescently labeled antibody coupled with light microscopic, flow cytometric, or fluorimetric detection.

[498] The antibodies (or fragments thereof), and/or polypeptides of the present invention may, additionally, be employed histologically, as in immunofluorescence, immunoelectron microscopy or non-immunological assays, for in situ detection of gene products or conserved variants or peptide fragments thereof. In situ detection may be accomplished by removing a histological specimen from a patient, and applying thereto a labeled antibody or polypeptide of the present invention. The antibody (or fragment thereof) or polypeptide is preferably applied by overlaying the labeled antibody (or fragment) onto a biological sample. Through the use of such a procedure, it is possible to determine not only the presence of the gene product, or conserved variants or peptide fragments, or polypeptide binding, but also its distribution in the examined tissue. Using the present invention, those of ordinary skill will readily perceive that any of a wide variety of histological methods (such as staining procedures) can be modified in order to achieve such in situ detection.

[499] Immunoassays and non-immunoassays for gene products or conserved variants or peptide fragments thereof will typically comprise incubating a sample, such as a biological fluid, a tissue extract, freshly harvested cells, or lysates of cells which have been incubated in cell culture, in the presence of a detectably labeled antibody capable of binding gene products or conserved variants or peptide fragments thereof, and detecting the bound

antibody by any of a number of techniques well-known in the art.

[500] The biological sample may be brought in contact with and immobilized onto a solid phase support or carrier such as nitrocellulose, or other solid support which is capable of immobilizing cells, cell particles or soluble proteins. The support may then be washed with suitable buffers followed by treatment with the detectably labeled antibody or detectable polypeptide of the invention. The solid phase support may then be washed with the buffer a second time to remove unbound antibody or polypeptide. Optionally the antibody is subsequently labeled. The amount of bound label on solid support may then be detected by conventional means.

[501] By "solid phase support or carrier" is intended any support capable of binding an antigen or an antibody. Well-known supports or carriers include glass, polystyrene, polypropylene, polyethylene, dextran, nylon, amylases, natural and modified celluloses, polyacrylamides, gabbros, and magnetite. The nature of the carrier can be either soluble to some extent or insoluble for the purposes of the present invention. The support material may have virtually any possible structural configuration so long as the coupled molecule is capable of binding to an antigen or antibody. Thus, the support configuration may be spherical, as in a bead, or cylindrical, as in the inside surface of a test tube, or the external surface of a rod. Alternatively, the surface may be flat such as a sheet, test strip, etc. Preferred supports include polystyrene beads. Those skilled in the art will know many other suitable carriers for binding antibody or antigen, or will be able to ascertain the same by use of routine experimentation.

[502] The binding activity of a given lot of antibody or antigen polypeptide may be determined according to well known methods. Those skilled in the art will be able to determine operative and optimal assay conditions for each determination by employing routine experimentation.

[503] In addition to assaying polypeptide levels or polynucleotide levels in a biological sample obtained from an individual, polypeptide or polynucleotide can also be detected *in vivo* by imaging. For example, in one embodiment of the invention, polypeptides and/or antibodies of the invention are used to image diseased cells, such as neoplasms. In another embodiment, polynucleotides of the invention (e.g., polynucleotides complementary to all or a portion of an mRNA) and/or antibodies (e.g., antibodies directed to any one or a combination of the epitopes of a polypeptide of the invention, antibodies directed to the full

length polypeptide expressed on the cell surface of a mammalian cell) are used to image diseased or neoplastic cells.

[504] Antibody labels or markers for in vivo imaging of polypeptides of the invention include those detectable by X-radiography, NMR, MRI, CAT-scans or ESR. X-radiography, suitable labels include radioisotopes such as barium or cesium, which emit detectable radiation but are not overtly harmful to the subject. Suitable markers for NMR and ESR include those with a detectable characteristic spin, such as deuterium, which may be incorporated into the antibody by labeling of nutrients for the relevant hybridoma. Where in vivo imaging is used to detect enhanced levels of polypeptides for diagnosis in humans, it may be preferable to use human antibodies or "humanized" chimeric monoclonal Such antibodies can be produced using techniques described herein or antibodies. otherwise known in the art. For example methods for producing chimeric antibodies are See, for review, Morrison, Science 229:1202 (1985); Oi et al., known in the art. BioTechniques 4:214 (1986); Cabilly et al., U.S. Patent No. 4,816,567; Taniguchi et al., EP 171496; Morrison et al., EP 173494; Neuberger et al., WO 8601533; Robinson et al., WO 8702671; Boulianne et al., Nature 312:643 (1984); Neuberger et al., Nature 314:268 (1985).

[505] Additionally, any polypeptides of the invention whose presence can be detected, can be administered. For example, polypeptides of the invention labeled with a radio-opaque or other appropriate compound can be administered and visualized *in vivo*, as discussed, above for labeled antibodies. Further, such polypeptides can be utilized for *in vitro* diagnostic procedures.

[506] A polypeptide-specific antibody or antibody fragment which has been labeled with an appropriate detectable imaging moiety, such as a radioisotope (for example, ¹³¹I, ¹¹²In, ^{99m}Tc), a radio-opaque substance, or a material detectable by nuclear magnetic resonance, is introduced (for example, parenterally, subcutaneously or intraperitoneally) into the mammal to be examined for a disorder. It will be understood in the art that the size of the subject and the imaging system used will determine the quantity of imaging moiety needed to produce diagnostic images. In the case of a radioisotope moiety, for a human subject, the quantity of radioactivity injected will normally range from about 5 to 20 millicuries of ^{99m}Tc. The labeled antibody or antibody fragment will then preferentially accumulate at the location of cells which contain the antigenic protein. *In vivo* tumor imaging is described in S.W. Burchiel et al., "Immunopharmacokinetics of Radiolabeled

Antibodies and Their Fragments" (Chapter 13 in *Tumor Imaging: The Radiochemical Detection of Cancer*, S.W. Burchiel and B. A. Rhodes, eds., Masson Publishing Inc. (1982)).

[507] With respect to antibodies, one of the ways in which an antibody of the present invention can be detectably labeled is by linking the same to a reporter enzyme and using the linked product in an enzyme immunoassay (EIA) (Voller, A., "The Enzyme Linked Immunosorbent Assay (ELISA)", 1978, Diagnostic Horizons 2:1-7, Microbiological Associates Quarterly Publication, Walkersville, MD); Voller et al., J. Clin. Pathol. 31:507-520 (1978); Butler, J.E., Meth. Enzymol. 73:482-523 (1981); Maggio, E. (ed.), 1980, Enzyme Immunoassay, CRC Press, Boca Raton, FL,; Ishikawa, E. et al., (eds.), 1981, Enzyme Immunoassay, Kgaku Shoin, Tokyo). The reporter enzyme which is bound to the antibody will react with an appropriate substrate, preferably a chromogenic substrate, in such a manner as to produce a chemical moiety which can be detected, for example, by spectrophotometric, fluorimetric or by visual means. Reporter enzymes which can be used to detectably label the antibody include, but are not limited to, malate dehydrogenase, staphylococcal nuclease, delta-5-steroid isomerase, yeast alcohol dehydrogenase, alphaglycerophosphate, dehydrogenase, triose phosphate isomerase, horseradish peroxidase, alkaline phosphatase, asparaginase, glucose oxidase, beta-galactosidase, ribonuclease, urease, catalase, glucose-6-phosphate dehydrogenase, glucoamylase and acetylcholinesterase. Additionally, the detection can be accomplished by colorimetric methods which employ a chromogenic substrate for the reporter enzyme. Detection may also be accomplished by visual comparison of the extent of enzymatic reaction of a substrate in comparison with similarly prepared standards.

[508] Detection may also be accomplished using any of a variety of other immunoassays. For example, by radioactively labeling the antibodies or antibody fragments, it is possible to detect polypeptides through the use of a radioimmunoassay (RIA) (see, for example, Weintraub, B., Principles of Radioimmunoassays, Seventh Training Course on Radioligand Assay Techniques, The Endocrine Society, March, 1986, which is incorporated by reference herein). The radioactive isotope can be detected by means including, but not limited to, a gamma counter, a scintillation counter, or autoradiography.

[509] It is also possible to label the antibody with a fluorescent compound. When the fluorescently labeled antibody is exposed to light of the proper wave length, its presence

can then be detected due to fluorescence. Among the most commonly used fluorescent labeling compounds are fluorescein isothiocyanate, rhodamine, phycocrythrin, phycocrythrin, allophycocrythrin, ophthaldehyde and fluorescamine.

[510] The antibody can also be detectably labeled using fluorescence emitting metals such as ¹⁵²Eu, or others of the lanthanide series. These metals can be attached to the antibody using such metal chelating groups as diethylenetriaminepentacetic acid (DTPA) or ethylenediaminetetraacetic acid (EDTA).

[511] The antibody also can be detectably labeled by coupling it to a chemiluminescent compound. The presence of the chemiluminescent-tagged antibody is then determined by detecting the presence of luminescence that arises during the course of a chemical reaction. Examples of particularly useful chemiluminescent labeling compounds are luminol, isoluminol, theromatic acridinium ester, imidazole, acridinium salt and oxalate ester.

[512] Likewise, a bioluminescent compound may be used to label the antibody of the present invention. Bioluminescence is a type of chemiluminescence found in biological systems in, which a catalytic protein increases the efficiency of the chemiluminescent reaction. The presence of a bioluminescent protein is determined by detecting the presence of luminescence. Important bioluminescent compounds for purposes of labeling are luciferin, luciferase and aequorin.

Methods for Detecting Diseases

[513] In general, a disease may be detected in a patient based on the presence of one or more proteins of the invention and/or polynucleotides encoding such proteins in a biological sample (for example, blood, sera, urine, and/or tumor biopsies) obtained from the patient. In other words, such proteins may be used as markers to indicate the presence or absence of a disease or disorder, including cancer and/or as described elsewhere herein. In addition, such proteins may be useful for the detection of other diseases and cancers. The binding agents provided herein generally permit detection of the level of antigen that binds to the agent in the biological sample. Polynucleotide primers and probes may be used to detect the level of mRNA encoding polypeptides of the invention, which is also indicative of the presence or absence of a disease or disorder, including cancer. In general, polypeptides of the invention should be present at a level that is at least three fold higher in diseased tissue than in normal tissue.

[514] There are a variety of assay formats known to those of ordinary skill in the art for using a binding agent to detect polypeptide markers in a sample. See, e.g., Harlow and Lane, *supra*. In general, the presence or absence of a disease in a patient may be determined by (a) contacting a biological sample obtained from a patient with a binding agent; (b) detecting in the sample a level of polypeptide that binds to the binding agent; and (c) comparing the level of polypeptide with a predetermined cut-off value.

[515] In a preferred embodiment, the assay involves the use of a binding agent(s) immobilized on a solid support to bind to and remove the polypeptide of the invention from the remainder of the sample. The bound polypeptide may then be detected using a detection reagent that contains a reporter group and specifically binds to the binding agent/polypeptide complex. Such detection reagents may comprise, for example, a binding agent that specifically binds to the polypeptide or an antibody or other agent that specifically binds to the binding agent, such as an anti-immunoglobulin, protein G, protein A or a lectin. Alternatively, a competitive assay may be utilized, in which a polypeptide is labeled with a reporter group and allowed to bind to the immobilized binding agent after incubation of the binding agent with the sample. The extent to which components of the sample inhibit the binding of the labeled polypeptide to the binding agent is indicative of the reactivity of the sample with the immobilized binding agent. Suitable polypeptides for use within such assays include polypeptides of the invention and portions thereof, or antibodies, to which the binding agent binds, as described above.

The solid support may be any material known to those of skill in the art to which polypeptides of the invention may be attached. For example, the solid support may be a test well in a microtiter plate or a nitrocellulose or other suitable membrane. Alternatively, the support may be a bead or disc, such as glass fiberglass, latex or a plastic material such as polystyrene or polyvinylchloride. The support may also be a magnetic particle or a fiber optic sensor, such as those disclosed, for example, in U.S. Patent No. 5,359,681. The binding agent may be immobilized on the solid support using a variety of techniques known to those of skill in the art, which are amply described in the patent and scientific literature. In the context of the present invention, the term "immobilization" refers to both noncovalent association, such as adsorption, and covalent attachment (which may be a direct linkage between the agent and functional groups on the support or may be a linkage by way of a cross-linking agent). Immobilization by adsorption to a well in a microtiter plate or to a membrane is preferred. In such cases, adsorption may be achieved by

contacting the binding agent, in a suitable buffer, with the solid support for the suitable amount of time. The contact time varies with temperature, but is typically between about 1 hour and about 1 day. In general, contacting a well of plastic microtiter plate (such as polystyrene or polyvinylchloride) with an amount of binding agent ranging from about 10 ng to about 10 ug, and preferably about 100 ng to about 1 ug, is sufficient to immobilize an adequate amount of binding agent.

[517] Covalent attachment of binding agent to a solid support may generally be achieved by first reacting the support with a bifunctional reagent that will react with both the support and a functional group, such as a hydroxyl or amino group, on the binding agent. For example, the binding agent may be covalently attached to supports having an appropriate polymer coating using benzoquinone or by condensation of an aldehyde group on the support with an amine and an active hydrogen on the binding partner (see, e.g., Pierce Immunotechnology Catalog and Handbook, 1991, at A12-A13).

Gene Therapy Methods

[518] Also encompassed by the invention are gene therapy methods for treating or preventing disorders, diseases and conditions. The gene therapy methods relate to the introduction of nucleic acid (DNA, RNA and antisense DNA or RNA) sequences into an animal to achieve expression of the polypeptide of the present invention. This method requires a polynucleotide which codes for a polypeptide of the present invention operatively linked to a promoter and any other genetic elements necessary for the expression of the polypeptide by the target tissue. Such gene therapy and delivery techniques are known in the art, see, for example, WO90/11092, which is herein incorporated by reference.

Thus, for example, cells from a patient may be engineered with a polynucleotide (DNA or RNA) comprising a promoter operably linked to a polynucleotide of the present invention ex vivo, with the engineered cells then being provided to a patient to be treated with the polypeptide of the present invention. Such methods are well-known in the art. For example, see Belldegrun, A., et al., J. Natl. Cancer Inst. 85: 207-216 (1993); Ferrantini, M. et al., Cancer Research 53: 1107-1112 (1993); Ferrantini, M. et al., J. Immunology 153: 4604-4615 (1994); Kaido, T., et al., Int. J. Cancer 60: 221-229 (1995); Ogura, H., et al., Cancer Research 50: 5102-5106 (1990); Santodonato, L., et al., Human Gene Therapy 7:1-10 (1996); Santodonato, L., et al., Gene Therapy 4:1246-1255 (1997); and Zhang, J.-F. et

al., Cancer Gene Therapy 3: 31-38 (1996)), which are herein incorporated by reference. In one embodiment, the cells which are engineered are arterial cells. The arterial cells may be reintroduced into the patient through direct injection to the artery, the tissues surrounding the artery, or through catheter injection.

[520] As discussed in more detail below, the polynucleotide constructs can be delivered by any method that delivers injectable materials to the cells of an animal, such as, injection into the interstitial space of tissues (heart, muscle, skin, lung, liver, and the like). The polynucleotide constructs may be delivered in a pharmaceutically acceptable liquid or aqueous carrier.

[521] In one embodiment, the polynucleotide of the present invention is delivered as a naked polynucleotide. The term "naked" polynucleotide, DNA or RNA refers to sequences that are free from any delivery vehicle that acts to assist, promote or facilitate entry into the cell, including viral sequences, viral particles, liposome formulations, lipofectin or precipitating agents and the like. However, the polynucleotide of the present invention can also be delivered in liposome formulations and lipofectin formulations and the like can be prepared by methods well known to those skilled in the art. Such methods are described, for example, in U.S. Patent Nos. 5,593,972, 5,589,466, and 5,580,859, which are herein incorporated by reference.

The polynucleotide vector constructs used in the gene therapy method are preferably constructs that will not integrate into the host genome nor will they contain sequences that allow for replication. Appropriate vectors include pWLNEO, pSV2CAT, pOG44, pXT1 and pSG available from Stratagene; pSVK3, pBPV, pMSG and pSVL available from Pharmacia; and pEF1/V5, pcDNA3.1, and pRc/CMV2 available from Invitrogen. Other suitable vectors will be readily apparent to the skilled artisan.

[523] Any strong promoter known to those skilled in the art can be used for driving the expression of the polynucleotide sequence. Suitable promoters include adenoviral promoters, such as the adenoviral major late promoter; or heterologous promoters, such as the cytomegalovirus (CMV) promoter; the respiratory syncytial virus (RSV) promoter; inducible promoters, such as the MMT promoter, the metallothionein promoter; heat shock promoters; the albumin promoter; the ApoAI promoter; human globin promoters; viral thymidine kinase promoters, such as the Herpes Simplex thymidine kinase promoter; retroviral LTRs; the b-actin promoter; and human growth hormone promoters. The promoter also may be the native promoter for the polynucleotide of the present invention.

[524] Unlike other gene therapy techniques, one major advantage of introducing naked nucleic acid sequences into target cells is the transitory nature of the polynucleotide synthesis in the cells. Studies have shown that non-replicating DNA sequences can be introduced into cells to provide production of the desired polypeptide for periods of up to six months.

The polynucleotide construct can be delivered to the interstitial space of tissues [525] within the an animal, including of muscle, skin, brain, lung, liver, spleen, bone marrow, thymus, heart, lymph, blood, bone, cartilage, pancreas, kidney, gall bladder, stomach, intestine, testis, ovary, uterus, rectum, nervous system, eye, gland, and connective tissue. Interstitial space of the tissues comprises the intercellular, fluid, mucopolysaccharide matrix among the reticular fibers of organ tissues, elastic fibers in the walls of vessels or chambers, collagen fibers of fibrous tissues, or that same matrix within connective tissue ensheathing muscle cells or in the lacunae of bone. It is similarly the space occupied by the plasma of the circulation and the lymph fluid of the lymphatic channels. Delivery to the interstitial space of muscle tissue is preferred for the reasons discussed below. They may be conveniently delivered by injection into the tissues comprising these cells. They are preferably delivered to and expressed in persistent, non-dividing cells which are differentiated, although delivery and expression may be achieved in non-differentiated or less completely differentiated cells, such as, for example, stem cells of blood or skin fibroblasts. In vivo muscle cells are particularly competent in their ability to take up and express polynucleotides.

[526] For the naked nucleic acid sequence injection, an effective dosage amount of DNA or RNA will be in the range of from about 0.05 mg/kg body weight to about 50 mg/kg body weight. Preferably the dosage will be from about 0.005 mg/kg to about 20 mg/kg and more preferably from about 0.05 mg/kg to about 5 mg/kg. Of course, as the artisan of ordinary skill will appreciate, this dosage will vary according to the tissue site of injection. The appropriate and effective dosage of nucleic acid sequence can readily be determined by those of ordinary skill in the art and may depend on the condition being treated and the route of administration.

[527] The preferred route of administration is by the parenteral route of injection into the interstitial space of tissues. However, other parenteral routes may also be used, such as, inhalation of an aerosol formulation particularly for delivery to lungs or bronchial tissues, throat or mucous membranes of the nose. In addition, naked DNA constructs can be delivered to arteries during angioplasty by the catheter used in the procedure.